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Structural Effects and Neurofunctional Sequelae of Developmental Exposure to Psychotherapeutic Drugs: Experimental and Clinical Aspects

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***Abstract*——The advent of psychotherapeutic drugs has enabled management of mental illness and other neurological problems such as epilepsy in the general population, without requiring hospitalization. The success of these drugs in controlling symptoms has led to their widespread use in the vulnerable population of pregnant women as well, where the potential embryotoxicity of the drugs has to be weighed against the potential problems of the maternal neurological state. This review focuses on the developmental toxicity and neurotoxicity of five broad categories of widely available psychotherapeutic drugs: the neuroleptics, the antiepileptics, the antidepressants, the anxiolytics and mood stabilizers, and a newly emerging class of nonprescription drugs, the herbal remedies. A brief review of nervous system development during gestation and following parturition in mammals is provided, with a description of the development of neurochemical pathways that may be involved in the action of the psychotherapeutic agents. A thorough discussion of animal research and human clinical studies is used to determine the risk associated with the use of each drug category. The potential risks to the fetus, as demonstrated in well described neurotoxicity studies in animals, are contrasted with the often negative findings in the still limited human studies. The potential risk for the human fetus in the continued use of these chemicals without more adequate research is also addressed. The direction of future research using psychotherapeutic drugs should more closely parallel the methodology developed in the animal laboratories, especially since these models have already been used extremely successfully in specific instances in the investigation of neurotoxic agents.**

I. Introduction

The thalidomide disaster has heightened public awareness of the deleterious effects of medicinal drugs on the developing fetus, and most women prefer not to use any medication, if at all possible, during pregnancy. It is, however, believed that a large percentage of women (up to 90% according to some estimates; Altshuler and Szuba, 1994) take one or more drugs during pregnancy, and of these, psychoactive compounds account for at least one-third of the drugs (Table 1) (Ashton, 1991; Arnon et al., 2000). Psychiatric disorders, particularly mood and anxiety disorders, are common in women of reproductive age, and some cases may be first diagnosed during pregnancy (Altshuler and Szuba, 1994; Kuller et al., 1996). The evidence that many women develop or have recurrence of psychiatric diseases during pregnancy or lactation does not support the once hypothesized notion that emotional and psychological changes associated with maternity can confer protection against onset or relapse of such illnesses (Altshuler et al., 1996; Arnon et al., 2000). There is sufficient evidence that all psychotropic drugs readily cross the placenta to reach the fetus and may also be excreted into breast milk (Chisholm and Kuller, 1997; Arnon et al., 2000; Bar-Oz et al., 2000). Drugs in the fetus may have a higher unbound free fraction, easily penetrate into the brain, and undergo only limited hepatic and/or extrahepatic metabolism (Arnon et al., 2000; Hines and McCarver, 2002; McCarver and Hines, 2002). Thus, the decision to initiate or continue pharmacotherapy during pregnancy and puerperium requires thoughtful weighing of the potential adverse effects of embryo, fetus, or infant exposure to psychotherapeutic drugs against the risks, for both mother and offspring, of untreated mental disorders (Altshuler et al., 1996; Kuller et al., 1996; Koren et al., 1998).

New drugs are typically not tested before marketing in pregnant women to determine effects on the fetus, although developmental toxicology and teratology studies in animals are required (Koren et al., 1998). Typically, a general statement is made such as "Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus" (Koren et al., 1998). For a number of psychotherapeutic drugs, harmful effects on the developing embryo, fetus, and child are known, but for several others there is still insufficient information. Potential adverse effects on embryonic, fetal, and neonatal development induced by exposure to pharmacotherapy include classic teratogenicity as well as more subtle developmental effects. Teratogenicity is usually associated with structural abnormalities induced by exogenous compounds during organogenesis; thalidomide, which caused severe limb defects and other organ dysgenesis, or isotretinoin, which caused a wide variety of CNS[1], craniofacial, and cardiovascular defects represent two examples of classic teratogens.

The fields of behavioral teratology and neurobehavioral toxicology have arisen during the past 30 years to allow researchers, particularly those using animal models of perinatal exposure to chemicals, to examine with well defined methodologies the more subtle and more long-lasting effects of such exposure. These methodologies, described in detail by various authors (Annau, 1986; Riley and Vorhees, 1986; Cuomo et al., 1996, Bignami, 1996), have proven to be extremely useful in revealing subtle postnatal effects of prenatal toxic expo-

[1]Abbreviations: CNS, central nervous sysytem; GAD, glutamate decarboxylase; GD, gestational day; PD, postnatal day; 5-HT, 5-hydroxytryptamine (serotonin); LC, locus coeruleus; NE, norepinephrine; NET, norepinephrine transporter; IQ, intelligence quotient; BZD, benzodiazepine; BDNF, brain-derived neurotrophic factor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; MAO, monoamine oxidase; REM, rapid eye movement (sleep).

TABLE 1
Major mental disorders and drugs commonly used in their treatment

Disorder	Drugs or Class of Drugs
Bipolar disorders	Anticonvulsants
	Benzodiazepines
	Conventional neuroleptics
	Lithium
	Novel neuroleptics
Depressive disorders	Anticonvulsants
	Atypical antidepressants
	Azapirones
	Benzodiazepines
	Lithium
	Monoamine oxidase inhibitors
	Selective serotonin reuptake inhibitors
	Selective norepinephrine reuptake inhibitors
	Selective serotonin norepinephrine reuptake inhibitors
	Tricyclic and tetracyclic compounds
Generalized anxiety disorders	Azapirones
	Barbiturates
	Benzodiazepines
	Novel neuroleptics
	Selective serotonin reuptake inhibitors
	Selective serotonin norepinephrine reuptake inhibitors
	Tricyclic and tetracyclic compounds
	Trazodone
Obsessive compulsive disorders	Novel neuroleptics (olanzapine, risperidone)
	Selective serotonin reuptake inhibitors
	Tricyclic and tetracyclic compounds
Panic disorders (with or without agoraphobia)	Benzodiazepines
	Monoamine oxidase inhibitors
	Selective serotonin reuptake inhibitors
	Tricyclic and tetracyclic compounds
Phobias	Benzodiazepines
	Clomipramine
	Monoamine oxidase inhibitors
	Selective serotonin reuptake inhibitors
Post-traumatic stress disorders	Monoamine oxidase inhibitors
	Selective serotonin reuptake inhibitors
	Tricyclic and tetracyclic compounds
Psychoses	Anticonvulsants
	Benzodiazepines
	Lithium
	Conventional neuroleptics (including phenothiazines, butyrophenones, thioxanthenes)
	Novel neuroleptics (including clozapine, olanzapine, quetiapine, risperidone)
Sleep disorders	Barbiturates
	Benzodiazepines
	Novel benzodiazepine-receptor agonists
	Trazodone

sures and, in conjunction with pharmacological challenges, in identifying underlying neurochemical alterations. These behavioral teratology studies have been applied in some instances to human populations, as in the case of lead (Needleman and Bellinger, 1994), but they have not yet become a required component of premarket testing of new pharmaceuticals. Given the vulnerability of the pregnant human population, it is difficult to conceive how premarket testing could be realized, but nevertheless, as the review of the literature will indicate, it is exactly the potential vulnerability of this population that needs to be addressed in the future. The types of behavioral effects most often observed in animal experiments following prenatal exposure to chemicals, in particular neurotoxic chemicals, are short- or long-term cognitive impairment, alterations in diurnal rhythms, emotional reactivity, and alterations of normal motor development. It is important to note that these behavioral effects can be seen in the offspring of treated mothers at doses that do not elicit either maternal toxicity or morphologic alterations in the neonates. Psychotherapeutic drugs, which target the CNS, are particularly prone to such neurofunctional/neurobehavioral teratogenic effects (Cuomo, 1987; Mantovani and Calamandrei, 2001). This review focuses on the effects of psychiatric drugs on the development of the fetus and the newborn. Animal and human studies are discussed, with an emphasis on structural teratogenic effects and biochemical and neurobehavioral alterations, as well as any data that may shed light on the mechanisms underlying developmental dysfunctions.

II. Neurotransmitters and Brain Development

To gain an understanding of the short- and long-term deleterious effects resulting from any interference with brain development, one must know the nature of the interference as well as the nature of the organ at the

time of insult (Rodier, 1980). From a large number of studies carried out mostly in rodents over the past 40 years, a great deal has been learned about the development of the brain (Dobbing and Sands, 1973; Dobbing, 1974; Rodier, 1980; Smart, 1991; Bayer et al., 1993). From these studies, one can infer the various stages of brain development in humans, although there are variations in the rates of brain growth among mammals, mostly dependent upon the length of gestation (Passingham, 1985; Bayer et al., 1993). Thus, the developmental ages of human and rat embryos or fetuses are comparable when major gross anatomical features and histological landmarks are similar in appearance in the two species, although their exact chronological ages are different (Bayer et al., 1993).

A first important general concept is that different parts of the central nervous system form at different stages of development; thus, there is not one critical (or safe) period, but many critical periods where exogenous compounds can exert deleterious effects. Using [^{3}H]thymidine autoradiography, the neurogenesis of specific populations of neurons was mapped in rodent brain, and extrapolations were made to the human brain (Rodier, 1980; Bayer et al., 1993). It is beyond the scope of this review to discuss these aspects in detail, except for pointing out that different brain areas develop at different times during gestation. Additionally, within a single brain region, subpopulations of neurons develop at different rates and at different times. Production of certain neurons can occur in very short intervals (a few days), whereas longer proliferative periods exist for other neurons (Rodier, 1980). For example, in the hippocampal region, neurons in the CA1 field develop on embryonic days 17 to 20 in the rat (corresponding to gestational weeks 7.5-15 in humans), whereas dentate granule cells develop later (embryonic day 20 to postnatal day 15 in the rat, corresponding to gestational weeks 15-36 in humans) (Bayer et al., 1993). In the cerebellum, Purkinje cells develop early (embryonic days 13-15 in the rat corresponding to 5-7 weeks in humans), whereas granule cells are generated much later (postnatal days 4-19 in rats, equivalent to gestational weeks 24-40 in humans) (Bayer et al., 1993).

An additional important aspect of brain development is the so-called "brain growth spurt," a transient period of growth when the brain is growing most rapidly (Dobbing and Sands, 1973). This occurs in the first 2 postnatal weeks in the rat and in the third trimester of pregnancy and in early infancy in humans (Dobbing, 1974). One of the general features of brain growth throughout mammalian species is that adult neuronal cell number is almost accomplished (with the notable exception of cerebellar granule cells and few other neurons), before the major phase of glial multiplication begins (Dobbing, 1974). The brain growth spurt is indeed characterized by rapid proliferation of glial cells, most notably astrocytes and oligodendrocytes. In addition to axonal myelination, this period also includes synaptogenesis and definition of the brain's cytoarchitecture. Most neurotransmitter systems do indeed develop during this time frame, including synthetic and degrading enzymes, uptake systems, and receptors (Coyle, 1977; Retz et al., 1996).

A very large number of studies have been published on the development of neurotransmitter systems, mostly in rodents. In general, levels of neurotransmitters are low at birth and reach adult levels by postnatal weeks 4 to 6 (Broening and Slikker, 1998). However, notable exceptions exist; for example, high levels of GABA and acetylcholine are already present at birth (Costa, 1993; De Blas, 1993). Enzymatic systems that synthesize neurotransmitters as well as uptake systems also develop during the first 3 to 4 postnatal weeks in the rat (Costa, 1993; Broening and Slikker, 1998; Varju et al., 2001), as do most receptor systems and receptor-activated signaling pathways (Jett, 1988; Duman and Alvaro, 1993; Costa, 1998; Vallano, 1998; Rho and Storey, 2001).

Thus, the development of neurotransmitter systems that may be targeted by psychotherapeutic drugs occurs mostly postnatally in the rat and coincides with synaptogenesis and the development of neurotransmission. However, various lines of evidence suggest that neurotransmitters may have several important roles in brain development in addition to neurotransmission (Buznikov, 1984; Lauder, 1988; Emerit et al., 1992; Johnston, 1995; Retz et al., 1996; Levitt et al., 1997; Contestabile, 2000; Nguyen et al., 2001). First, the appearance of one or more key components of neurotransmission may precede synaptogenesis; for example GABA, glutamate decarboxylase (GAD), and $GABA_A$ receptors are present in embryonic neurons well before the development of GABAergic synapses (Kim et al., 1996). Second, a transient overexpression of receptors at certain developmental stages, before a decrease to adult levels, as in the case, for example, of glutamate *N*-methyl-D-aspartate receptors or some dopamine receptors, suggests a role for certain neurotransmitters beyond neurotransmission itself (Retz et al., 1996; Broening and Slikker, 1998). Third, coupling of receptors to signal transduction systems may also show a peculiar developmental profile, as seen, for example, in the case of muscarinic and metabotropic glutamate receptor coupling to phospholipase C (Balduini et al., 1991; Costa, 1998).

Evidence for a number of roles of neurotransmitters in brain development has emerged from a variety of animal species and experimental in vitro and in vivo models, including transgenic animals as well as studies with selective neurotoxicants. Although a complete understanding of how neurotransmitters would ultimately shape brain development in vivo has still not been achieved, these studies clearly show that these molecules, in conjunction with growth factors and cytokines, can exert profound effects on the proliferation and maturation of neuronal and glial cells. Such effects range from modulation of proliferation of neuronal stem cells,

neuroblasts, and glioblasts (Azmitia, 2001; Nguyen et al., 2001; Varju et al., 2001), to regulation of migration and induction of differentiation (Retz et al., 1996; Levitt et al., 1997; Azmitia, 2001). Neurotransmitters can also act as trophic factors modulating the apoptotic processes that are known to occur at certain stages of brain development (Emerit et al., 1992; Ikonomidou et al., 2001). Such effects have been described for most neurotransmitter systems that may be affected by psychotherapeutic drugs, including serotonin (Emerit et al., 1992; Azmitia, 2001; Lesch, 2001; Nguyen et al., 2001; Okado et al., 2001; Rho and Storey, 2001), GABA (Levitt et al., 1997; Ikonomidou et al., 2001; Nguyen et al., 2001; Varju et al., 2001), dopamine (Levitt et al., 1997; Rho and Storey, 2001), norepinephrine (Duman and Alvaro, 1993; Rho and Storey, 2001), acetylcholine (Costa, 1993; Nguyen et al., 2001; Rho and Storey, 2001), and glutamate (McDonald and Johnston, 1990; Contestabile, 2000; Ikonomidou et al., 2001). The major classes of psychotherapeutic drugs target four neurotransmitter systems (dopamine, serotonin, norepinephrine, and GABA), and changes in various parameters of these systems have been reported in animals perinatally exposed to these drugs. Therefore their ontogenesis is discussed in more detail.

A. Dopaminergic System

Dopamine-containing cells can be detected in the rat brainstem by gestational day (GD) 12 or 13; soon after, they begin to sprout axons that reach the telencephalon at GD 14 (Voorn et al., 1988). Fibers arising from the substantia nigra and pars compacta can be visualized in the maturing striatum, including the primordium of nucleus accumbens, by GD 15 and 16 (Voorn et al., 1988). By GD 19, dopaminergic axons have traced out distinct pathways to most areas of dorsal and ventral striatum; at the same time, a patch-matrix type morphology can be recognized in the developing caudate putamen (Specht et al., 1981a,b). Fibers with varicosities in the striatum, already present at postnatal day (PD) 2, gradually increase through the first 2 weeks to achieve their adult feature by PD 21. Similarly, dopaminergic axons emerging from the ventral tegmental area reach the septum and the prefrontal cortex subplate at GD 16 and 17 and the cingulate cortex at GD 20 (Verney et al., 1982; Kalsbeek et al., 1988). Dopaminergic innervation to the neocortex starts resembling the adult pattern in density and distribution by PD 12. However, the adult morphology and organization are completely achieved only at the end of the first month of postnatal life (Kalsbeek et al., 1988).

Evidence that dopamine receptors are found early in brain development, before the formation of subcortical and cortical synaptic connections, suggests that dopamine, acting through its receptors, may play an important function in neural development (Todd, 1992; Castro et al., 1994; Swarzenski et al., 1994; Lidow and Wang, 1995). Convincing results suggest that, during brain maturation, dopamine may have a modulatory role in neuronal growth and in modeling neuronal and synaptic architecture (Lankford et al., 1988; Murrin and Zeng, 1990). In retinal neurons, stimulation of D_1 receptors inhibits neurite outgrowth (Lankford et al., 1988; Murrin and Zeng, 1990), whereas in cortical and mesencephalic neurons activation of D_2-like receptors increases the extension and branching of neurites (Todd, 1992). Moreover, stimulation of D_4 receptors results in the dramatic increase in neurite length in the transfected clonal specific MN9D cell line (Swarzenski et al., 1994). Density of D_1 dopamine receptors in rat striatum is approximately 10% of the adult value at birth (Jung and Bennett, 1996). During postnatal development, a steady increase in the density of both D_1 and D_2 dopamine receptor subtypes occurs, with a greater prevalence of D_1 and D_2 dopamine receptor binding sites around the time of weaning (Murrin, 1986;Gelbard et al., 1989; Murrin and Zeng, 1990; Rao et al., 1991). By the end of the second postnatal week, D_1 receptor density begins to approximate the adult value (Leslie et al., 1991). Evidence also exists that D_1 receptors in the prefrontal cortex achieve the adult topological pattern and density early after the birth (Leslie et al., 1991). Studies examining the ontogeny of dopamine D_2 receptors have reported that significant levels of receptors are expressed by PD 3, and adult levels are reached by PD 21 (Rao et al., 1991). Forebrain dopamine D_3 receptors appear to be expressed later in development than D_2 receptors in the same regions. Dopamine D_3 binding sites are absent at PD 3 and just detectable at PD 7 and PD 10. Appreciable D_3 labeling appears in the islands of Calleja at PD 14 and in the nucleus accumbens at PD 21 (Demotes-Mainard et al., 1996; Stanwood et al., 1997). Using the polymerase chain reaction technique, it has been reported that the developmental ontogeny of D_4 receptor mRNA does not correlate with the ontogeny of the D_2 dopamine receptor mRNA. Indeed, the level of expression of the D_4 receptor mRNA is appreciable at birth, increases to a maximum at PD 3, and declines at PD 28, whereas levels of dopamine D_2 receptor mRNA are highest on PD 28 (Nair and Mishra, 1995). Information on the expression of D_5 dopamine receptors in the embryonic rat brain is still insufficient; however, in the fetal primate brain, many cortical cells express D_1 and D_5 dopamine receptors (Lidow and Wang, 1995; Wang et al., 1997a). Dopamine D_1 and D_5 receptors are differently distributed, suggesting that they may play different roles in cerebral developmental processes. In particular, as D_5 dopamine receptors have a higher affinity for dopamine then D_1 receptors, they may be more suitable for nonsynaptic interactions, given the low level of dopamine present in the intercellular space of the fetal brain (Lidow, 1995; Lidow and Wang, 1995; Wang et al., 1997a).

B. Serotonergic System

Similar to dopamine, the early expression of serotonin [5-hydroxytryptamine (5-HT)] and its receptors in the developing brain has brought attention to its potential contribution in modulating neuronal developmental processes. In this context, it has been reported that parachlorophenylalanine, a 5-HT synthesis inhibitor, retarded neuronal maturation (Lauder and Krebs, 1978), and that the transient excess of serotonin during prenatal life in knock-out mice lacking monoamino-oxidase A resulted in a disrupted bamfield organization in the primary somatosensory cortex (Cases et al., 1996). In vitro experiments have shown that 5-HT regulates neuritic growth and synapse formation (Chubakov et al., 1986; Haydon et al., 1987). In undifferentiated neuroblastoma cells, high levels of 5-HT (50 μM) induce a decrease, whereas low levels (50 nM) induce an increase in the cytoplasmic *tau* protein (John et al., 1991). Thus, there is evidence that 5-HT plays a role in a variety of cellular processes involved in regulating metabolism, proliferation, and morphology of neurons. The fine integration of these dynamic events appears to involve multiple receptor action. Serotonergic neurons begin to sprout axons by GD 15 (Lidov and Molliver, 1982a,b; Wallace and Lauder, 1983). These axons grow rapidly, and by GD 17 serotonergic axons enter the basal forebrain, with some fibers reaching as far forward as the septum and the frontal pole of the neocortex (Lauder et al., 1982; Lidov and Molliver, 1982a; Wallace and Lauder, 1983). By GD 19 serotonergic axons have established pathways to all major divisions of the forebrain in the rat (Wallace and Lauder, 1983). Axon pathways increase in density, and terminal fields begin to appear by GD 21 (Lidov and Molliver, 1982a). Terminal field innervation continues into the postnatal developmental period and is the main feature of postnatal serotonergic development. By PD 3, elaboration of the serotonergic neuropil is underway in most cortical regions and in the hippocampus (Lidov and Molliver, 1982a; Dori et al., 1996). At this developmental stage, innervation in most brainstem regions is quite dense, and patterns of innervation have begun to resemble those present in the adult.

In the rat, whole-brain 5-HT_1 serotonergic receptor density is approximately 45% of the adult value at birth, but it is only 24% in the frontal cortex (Zilles et al., 1985). Several subtypes of 5-HT_1 receptors have been identified, including the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors (Hoyer et al., 1994). The 5-HT_{1A} receptor develops early in the CNS and is associated with secretion of S-100β from astrocytes and reduction of cAMP levels in neurons. These actions provide intracellular stability for the cytoskeleton and result in cell differentiation and cessation of proliferation (Azmitia, 2001). In cerebral cortex, 5-HT_{1B} receptor density is 31% of the adult value at 5 days of age and reaches 65% of the adult value by 3 weeks. Whole-brain 5-HT_{2A} serotonergic receptor density is low in the perinatal period (17% of the adult value 2 days after birth) (Bruinink et al., 1983; Roth et al., 1991) but reaches 76% of the adult value at 2 weeks, and 100% at 4 weeks of age. Thus, 5-HT_{2A} receptors develop more slowly and are associated with glycogenolysis in astrocytes and increased calcium availability in neurons. These actions destabilize the internal cytoskeleton and result in cell proliferation, synaptogenesis, and apoptosis (Azmitia, 2001). Whole-brain 5-HT_{2C} receptor density reaches adult values by PD 5 (Roth et al., 1991). However, 5-HT_{2C} receptor density in cerebral cortex is only approximately 24% of the adult value at PD 1 and reaches 37% of the adult value by PD 10, 76% of the adult value by 2 weeks, and adult values by 3 weeks of age (Pranzatelli, 1993).

The development of the high-affinity 5-HT reuptake transporter has been studied by measuring [^{3}H]5-HT uptake and [^{3}H]paroxetine binding. Cortical [^{3}H]5-HT uptake ranges from 19 to 22% of the adult value at birth (Kirksey and Slotkin, 1979; Huether et al., 1992) and reaches 42 to 54% of the adult value by 2 weeks of age; by 4 to 5 weeks of age, [^{3}H]5-HT uptake in the cortex approaches adult values. Investigation of the ontogeny of the high-affinity [^{3}H]5-HT uptake transporter by [^{3}H]paroxetine binding discloses a somewhat faster developmental time course compared with that observed in studies using [^{3}H]5-HT uptake. Indeed, cortical [^{3}H]paroxetine binding to the 5-HT uptake transporter is 39% of the adult values by the end of the first postnatal week and reaches the adult value by 2 weeks of age (Pranzatelli and Martens, 1992). The widespread distribution of the 5-HT transporter during ontogeny, regulating 5-HT levels in the neuronal microenvironment, confirms the important role of serotonin in diverse physiological processes during embryonic development. If 5-HT is indeed widely expressed in embryos, teratogenic effects or more severe neurofunctional sequelae would be expected as a result of in utero exposure to agents able to inhibit its function. Although only limited evidence for detrimental effects in intact animals or in humans is currently available, effects might be seen later or be more subtle, or perturbation of the serotonin system might result in compensatory responses either in the 5-HT system or in interacting related systems. However, it has been reported that 5-HT transporter-deficient mice do not exhibit any alteration, even if there are compensatory changes in the 5-HT system, with a desensitized response to the 5-HT_{1A} agonists despite normal levels of receptors (Wichems et al., 1997).

C. Noradrenergic System

Noradrenergic innervation from the locus coeruleus (LC) occurs very early in the development of mammalian brain (Levitt and Moore, 1978). In the rat, noradrenergic neurons differentiate at or before GD 12 and give rise to projections shortly thereafter (Specht et al., 1981),

reaching their destination before the differentiation of target neurons (Schlumpf et al., 1980). Because of the early presence of norepinephrine (NE) in the developing brain, it has been suggested that the adrenergic system regulates several aspects of pre- and postnatal brain development, including cell division, neuronal maturation, synaptogenesis, and physiological plasticity (Blue and Parnavelas, 1982; Slotkin et al., 1988, 1994). Axons arise from the noradrenergic perikarya in the developing LC at GD 14. By GD 15, these axons extend into the ventral mesencephalon and the dorsal pons to form the nascent ventral and dorsal noradrenergic bundles, respectively (Specht et al., 1981). Noradrenergic axons simultaneously innervate the medial and lateral cortex at this age; however, the dorsal cortex is not innervated until GD 19 (Levitt and Moore, 1978; Berger and Verney, 1984; Verney et al., 1984). GD 18 first identifies noradrenergic fibers identified in the hippocampus. Noradrenergic axons move laterally under the anterior commissure at GD 20 and yield the marginal and intermediate zones of the lateral frontal cortex. Medially, noradrenergic axons course through the dorsal diagonal band and rostrally to it via the developing medial forebrain bundle (Levitt and Moore, 1978; Verney et al., 1984). On arriving to the corpus callosum, these axons diverge into two axon bundles: one running above the corpus callosum penetrating the cingulate cortex, and the other coursing below the corpus callosum and entering the septum (Berger et al., 1983; Verney et al., 1984). The morphology of the noradrenergic axons begins to modify from thick, straight fibers to thin, varicose fibers by GD 20 (Berger and Verney, 1984; Verney et al., 1984). Noradrenergic fibers innervate all layers of the neocortex by PD 7 (Lidov et al., 1978; Levitt and Moore, 1979; Verney et al., 1982; Berger et al., 1983), and noradrenergic innervation to this brain area resembles that of adults by PD 14 (Levitt and Moore, 1979; Berger et al., 1983). Thus, noradrenergic innervation to the forebrain matures at an earlier age than the dopaminergic and serotoninergic innervation to the forebrain.

Whole-brain NE uptake ranges from 13 to 30% of the adult value at birth (Coyle and Axelrod, 1971; Kirksey et al., 1978) and increases rapidly, so that 70 to 100% of the adult value is reached by the end of the second postnatal week. Cortical [^{3}H]NE uptake also develops early during postnatal life in the rat, which is compatible with the early innervation of the cortex by noradrenergic fibers. Cortical [^{3}H]NE uptake ranges from 13 to 15% of the adult value at birth (Levitt and Moore, 1979) and reaches adult values by the end of the third postnatal week. There may also be a short-lasting overexpression of [^{3}H]NE uptake in frontal cortex, as uptake in this brain region has been reported to exceed 200% of the adult value at 2 weeks of age (Levitt and Moore, 1979). It has been recently reported that fibroblast growth factor-2, neurotrophin-3, and transforming growth factor-β1 regulate norepinephrine transporter (NET) expression in cultured neural crest cells by causing an increase in NET mRNA levels (Sieber-Blum and Ren, 2000). They also promote NET function in both neural crest cells and presumptive noradrenergic cells of the LC. The growth factors are synthetized by the neural crest cells and, therefore, are likely to have autocrine functions. NE transport regulates differentiation of noradrenergic neurons in the peripheral nervous system and the LC by promoting expression of tyrosine-hydroxylase and dopamine-beta hydroxylase. Conversely, uptake inhibitors, such as the tricyclic antidepressants and other NET inhibitors, inhibit noradrenergic differentiation in both tissues. Thus, growing evidence suggests that: 1) NET is expressed early in embryonic development; 2) NE transport is involved in regulating expression of the noradrenergic phenotype in the peripheral and central nervous system; and 3) norepinephrine uptake inhibitors can deeply disturb noradrenergic cell differentiation in the sympathetic ganglion and LC (Sieber-Blum and Ren, 2000).

An increasing body of data indicates that α_1-adrenergic receptors are present in cultured rat cortical neurons at an early development stage. The number of α_1 clusters gradually increases on both cell bodies and neuronal processes in the culture environment from day 0 to day 20. Interestingly, it has been shown that their expression is developmentally regulated and that both neuronal activity and receptor occupancy influence receptor expression; however, neuronal activity dominates over receptor occupancy in the regulation of receptor expression (Wang et al., 1997b). The receptors are mainly expressed on the cell body in the early stages of the cortical cultures and later along neuronal processes. Moreover, receptor binding studies using [^{3}H]prazosin to label α_1-adrenergic receptors in the rat cerebral cortex have shown a progressive increase in receptor density during postnatal development (Schoepp and Rutledge, 1985; Slotkin et al., 1990), with 54% of adult value by 2 weeks and full adult value by 3 weeks of age (Schoepp and Rutledge, 1985; Slotkin et al., 1990). The α_{2A}-adrenoceptor subtype is widely expressed during periods of neuronal migration and differentiation throughout the developing brain; both α_{2A} receptor mRNA and protein expression are strongly expressed by GD 19 and GD 20, respectively (Winzer-Serhan et al., 1997a,b). The increased expression occurs in the cortical plate and intermediate and subventricular zones, corresponding to tiers of migrating and differentiating neurons. This transient up-regulation of α_{2A}-adrenoceptors is restricted to the lateral neocortex. At GD 20 functional α_{2A}-adrenoceptors are also detected in deep layers of lateral neocortex. During the first week of postnatal development, the expression of α_{2A} receptor mRNA and protein changes markedly, giving rise to a more mature pattern of anatomical distribution. The temporal and spatial distribution of α_{2A}-adrenoceptors in developing neocortex is consistent with expression of functional pro-

teins on migrating and differentiating layer IV to II neurons, suggesting that these receptors may mediate a neurotrophic effect of NE during fetal cortical development (Winzer-Serhan and Leslie, 1999). α_{2B} Receptor mRNA is transiently expressed in the developing vascular plexus during the time of neovascularization in the brain. Additionally, developmentally regulated expression is also detected in the caudate putamen and in the cerebellum, in a pattern which parallels the expression of α_{2A}- and α_{2C}-adrenoceptors in these structures (Winzer-Serhan and Leslie, 1997). Furthermore, the developmental pattern of α_{2C}-adrenoceptor mRNA and protein expression is in marked contrast to the early and transient expression of that of α_{2A}-receptor. There is no widespread expression of α_{2C}-adrenoceptor mRNA or protein in the fetal brain. Expression occurs during the postnatal period, after the major period of neuronal migration and differentiation, and is largely restricted to areas in which there is expression in the adult (Winzer-Serhan et al., 1997a,b). These findings suggest that α_{2C}-adrenoceptors do not play a relevant role in regulating developmental processes. This assumption is supported by the fact that α_{2C}-adrenoceptor-deficient mice do not exhibit any apparent behavioral or morphological defects (Link et al., 1995). Density of β-adrenoceptors in whole brain is low at birth (only 14% of the adult value) (Erdtsieck-Ernste et al., 1991), and adult values are reached by 3 weeks of age. A similar pattern of development also occurs in the cortex (Pittman et al., 1980; Lorton et al., 1988). In the adult, the β_1-adrenoceptor subtype represents approximately 80% of the total β-adrenoceptors present in the cortex. This relative proportion is also present during postnatal ontogeny, except for the perinatal period, when β_2 receptors provide a greater percentage to the total (Pittman et al., 1980; Erdtsieck-Ernste et al., 1991).

D. GABAergic System

γ-Aminobutyric acid (GABA) is one of the earliest substances to appear in the mammalian developing brain (Lauder et al., 1986; Miranda-Contreras et al., 1998). Three types of GABA receptors have been currently identified in the CNS: the $GABA_A$ and $GABA_C$, which are both ionotropic, and the metabotropic $GABA_B$ receptor (Chebib and Johnston, 1999). Furthermore, six different subunit families have been recognized to constitute CNS $GABA_A$ receptors: α 1–6, β 1–3, γ 1–3, δ, ϵ, and θ, whereas three additional subunits, ρ 1–3, have been distinguished as part of the $GABA_C$ receptor (Bormann and Feigenspan, 1995; Luddens et al., 1995).

The early appearance of GABA and its receptors during embryonic brain development, long before the onset of inhibitory synaptogenesis, led to the suggestion that it may play a maturative role before work as neurotransmitter (Lauder, 1993). If GABA serves critical developmental roles, then interference in this early functioning could influence the normal course of brain development. In the rat, GABA has been detectable at ED 12 in axons running through the brainstem (Lauder et al., 1986). In the spinal cord, mRNA encoding both isoforms GAD_{65} and GAD_{67} of the synthesizing enzyme glutamate decarboxylase have been detected at ED 11 (Somogyi et al., 1995). At ED 13 GABA-immunoreactive fibers have been found to project from spinal cord and brainstem toward midbrain and diencephalons (Lauder et al., 1986), whereas at ED14 GABAergic cells have been identified in the lateral cortex and by ED 16 in the basal forebrain and all regions of the primitive cortex. Such cortical cells are located in the marginal and intermediate zones as well as in the subplate (Van Eden et al., 1989). Additional cells are also located in the ventricular and subventricular zones of the neocortex at ED 16 to 17. GABA neurons remain in the subplate during most part of pregnancy and spread over cortical plate by ED 18 (Cobas et al., 1991). During corticogenesis GABA neurons are located in the marginal zone and subplate to contact migrating neurons and affect cortical afferent development (Meinecke and Rakic, 1992; Lauder, 1993). By birth in rats, a well expanded axonal plexus is recognizable around maturating hippocampal cells (Lubbers and Frotscher, 1988). Similarly, in the postnatal cerebellum GAD-immunoreactive fibers encompass differentiating granule cells (Lauder, 1993), suggesting that GABA may play a role in granule cell maturation both in cerebellum and hippocampus.

Functional $GABA_A$ receptors are detectable on mitotically active precursor elements in the neocortical proliferative zone (LoTurco et al., 1991; Owens et al., 1999). They display a major affinity for GABA and appear rather insensitive to receptor desensitization processes (Owens et al., 1999). Such functional dissimilarities in $GABA_A$ receptor functioning in precursor elements and postmitotic neurons might derive from the discrepancy in subunit composition (Araki et al., 1992; Poulter et al., 1993). Indeed, in the embryonic cortical plate, where postmitotic neurons are predominantly located, $\alpha 3/\beta 2$-$\beta 3$ and $\gamma 3$ subunits have been found to predominate (Ma and Barker, 1995).

Whereas in the adult brain $GABA_A$ receptor activation has been related to the mediation of synaptic inhibition, in immature neurons this causes marked membrane depolarization that can induce action potential discharge (Ben-Ari et al., 1989; Owens et al., 1996, 1999; Dammerman et al., 2000; Gao and van den Pol, 2001). The relatively higher intracellular chloride concentration is considered responsible for the observed response (Ben-Ari et al., 1989; Chen et al., 1996; Rohrbough and Spitzer, 1996). With further development, chloride concentration declines so that the effect of GABA becomes increasingly inhibitory (Owens et al., 1996). During the period of active neurogenesis and until about the first postnatal week, the activation of $GABA_A$ receptors has been shown to induce membrane depolarization and a rise in cytosolic Ca^{2+} (Cherubini et al., 1991; LoTurco et

al., 1995; Owens et al., 1996, 1999). The activation of voltage-dependent Ca^{2+} channels occurring during depolarization has been thought to contribute to the elevation in intracellular Ca^{2+} (Leinekugel et al., 1995; Ben-Ari, 2002). These findings have suggested that one potential consequence of $GABA_A$ receptor in maturing neurons is the activation of Ca^{2+}-dependent second messenger pathways (Cherubini et al., 1991), which in turn can affect a variety of processes, including proliferation, synaptogenesis, and circuit modeling.

With regard to $GABA_B$ receptors, immunohistochemical studies have shown that both R1 and R2 subunits are present in the embryonic cortex, and $GABA_B$ receptor activation can influence the movement of immature cortical neurons. However, functional $GABA_B$ receptor-mediated postsynaptic responses have been reported that do not occur in the neocortex until after the second postnatal week (Luhmann and Prince, 1991), although it has been observed that presynaptic receptor activation occurs by the first week (Fukuda et al., 1993).

Experimental evidence has shown that GABA triggers signals in proliferating cells located in the telencephalic ventricular zone, functioning as a modulator of cell proliferation (LoTurco et al., 1995; Owens et al., 1999; Haydar et al., 2000). Investigating [^{3}H]thymidine or bromodeoxyuridine incorporation in cells derived from the ED 16 to 19 cortex has demonstrated that GABA can influence DNA synthesis in proliferating cells (LoTurco et al., 1995). Moreover, GABA has been reported to prevent exit from the cell cycle and to reduce cell cycle duration of cells from the ventricular zone of embryonic cortex. Studies on the migratory responses have disclosed that GABA may stimulate directed migration (chemotaxis) of cells derived from ED 18 ventricular and subventricular zone, whereas facilitates chemokinesis (random motility) of more mature neurones derived from the cortical plate-subplate regions (Behar et al., 1996, 2000, 2001). Interestingly it has also been documented that $GABA_C$ and $GABA_B$ receptor activation in rats is able to promote migration out of the ventriculare zone and the intermediate zone, respectively, whereas $GABA_A$ receptor activation could provide a "stop signal," once cells have reached the cortical plate (Behar et al., 2000). The relevance of these results requires further evaluation, since factors others than GABA have been found implicated in the arrest of cell migration at the cortical plate (Dulabon et al., 2000; Supèr et al., 2000). Selectively antagonizing $GABA_C$ and $GABA_B$ receptor activation has resulted only in a delay but not in a complete arrest of migration, suggesting that, although GABA-mediated signaling could promote neuronal migration, it is not absolutely crucial for this process, since its absence may be physiologically compensated (Behar et al., 2000). The GABA-mediated migratory signals have been reported to act through Ca^{2+} transients that affect cell movements by altering the dynamics of cytoskeletal remodeling (Gomez and Spitzer, 1999). On the other hand, similar investigations in immature neurons from embryonic mouse brain have indicated that *N*-methyl-D-aspartate-type glutamate receptor, rather than GABA receptor, activation seems to affect migration, suggesting that a discrepancy exists between these two rodent species regarding the nature of signals moderating neuronal migration in immature brain (Varju et al., 2001; Owens and Kriegstein, 2002).

Current data seem to validate the hypothesis that in embryonic brain GABA acts by accelerating neuronal maturation and promoting formation of functional synapses (Varju et al., 2001). The transformation of a growth cone to a synaptic element implicates the maturation of the biochemical machinery of neurotransmission; this transition may be affected in part by changes in subunit composition of $GABA_A$ receptors (Maric et al., 1997; Owens et al., 1999) and probably involves switches in the expression of components implicated in GABA synthesis, storage, and release (Somogyi et al., 1995). GABA has been reported to enhance the density of intracellular organelle in rat cerebellar granule cells (Hansen et al., 1987), including the Golgi apparatus, rough endoplasmic reticulum, microtubules, and coated vesicles, and may stimulate metabolic activity of neurons. It has been also described that GABA up-regulates the expression of specific $GABA_A$ receptor subunits (α_1 and β_2), and promotes the synthesis of a number of neuron-specific proteins, including neuron-specific enolase and neural cell adhesion molecules (Belhage et al., 1998). In cultured embryonic hippocampal and neocortical neurons, $GABA_A$ receptor activation has been shown to stimulate neurite outgrowth and maturation of GABA interneurons (Barbin et al., 1993; Marty et al., 1996; Maric et al., 2001).

III. Antipsychotics and Antiepileptics

A. Antipsychotic Drugs

The annual incidence of psychosis in pregnant women has been reported to be 7.1 cases per 100,000 (Nurnberg, 1989), and epidemiological studies indicate that psychotic women neither recover nor require decreased doses of maintenance drugs during pregnancy (Trixler and Tényi, 1997). In addition, reducing or discontinuing medications in psychotic pregnant women responsive to treatment may result in a raised individual risk of relapse (Casiano and Hawkins, 1987). Thus, emotional and somatic changes occurring during gestation or puerperium do not protect from the development or the recurrence of psychosis. Although physicians often become hesitant when recommending antipsychotic drugs during pregnancy because of their potential fetotoxicity, avoiding medications is not usually possible. Indeed, withholding treatment for such mentally ill patients carries potentially serious consequences, as untreated psychosis may adversely influence the course of pregnancy (Kris, 1961). In addition, a recent study suggests

that emotional stress during organogenesis can cause congenital malformations, particularly those of cranial neural crest (Hansen et al., 2000). Thus, in all cases, clinicians must carefully weigh the risk of fetal exposure to antipsychotic medications against the potential adverse effects to both mother and fetus of untreated mental illness. The two major groups of antipsychotic drugs are the typical neuroleptics, such as phenothiazines, thioxanthenes, and butyrophenones; and the atypical neuroleptics, such as clozapine, risperidone, olanzapine, ziprasidone, and quetiapine.

1. Typical Antipsychotics. Typical neuroleptic agents act primarily by blocking brain dopamine receptors, and radioligand binding assays indicate that antipsychotic potency is highly correlated with affinity for D_2 dopamine receptors. These findings have been further strengthened by positron emission tomography data, which show that the effectiveness of typical neuroleptics is associated with an occupancy of 80% of D_2 dopamine receptors, whereas higher occupancy rates may be associated with more adverse effects, without greater effectiveness (Baldessarini and Tarazi, 2001). Although many standard neuroleptics, in particular thioxanthenes and phenothiazines, bind with relatively high affinity to other subtypes of dopamine receptors, as well as to other receptors, it appears that the antipsychotic effects of classic neuroleptics require D_2 receptor blockade, followed by a decreased dopaminergic activity.

About one third of the agents commonly used for the treatment of psychosis may exert teratogenic effects in laboratory animals. Several compounds can cause cleft palate in mice, without overt teratogenic activity in other species. These comprise, among others, fluphenazine, haloperidol, trifluperidol, and thioridazine (Vichi et al., 1968; Vichi, 1969; Szabo and Brent, 1974). Studies addressing phenothiazine teratogenicity in rats have yielded conflicting results (Jelinek et al., 1967; Clark et al., 1970; Beall, 1972; Singh and Padmanabam, 1978), whereas haloperidol causes increased incidence of fetal resorption, delayed delivery, and neonatal death at doses 2- to 10-fold higher than the maximum doses used in humans (Dollery, 1999).

Because of their small molecular size and relative lipophilicity, neuroleptics are assumed to readily cross the placenta and to enter fetal circulation (Pacifici and Nottoli, 1995). Data on fetal outcome for psychotic women treated with neuroleptics during gestation are limited, so the potential risks of antipsychotic exposure during pregnancy are still not fully known. Moreover, accumulating evidence suggests that children born to psychotic mothers may exhibit increased risks of abnormalities not related to neuroleptic exposure. Indeed, previous studies, comparing pregnant psychotic women with or without exposure to phenothiazines during gestation, reported the rate of fetal damage to be similar in both groups, but approximately twice that observed in the general population, suggesting that maternal psychiatric disease may constitute itself a risk factor for fetal anomalies (Sobel, 1960; Rieder et al., 1975). The mechanism underlying the increased risk related to the mental illness remains not comprehended, but investigators have pointed out that psychotic women often smoke, misuse other substances, are socioeconomically disadvantaged, and have poor compliance with prenatal care (Bennedsen, 1998).

Results on reproductive effects associated with gestational use of neuroleptics are conflicting, since many findings derive from retrospective and prospective studies, whose accuracy has been often questioned for inadequate attention to potential confounding variables, such as diagnosis and severity of the illness, dosage, maternal age, and exposure to other medications, as well as to alcohol and illicit drugs. Indeed, in most studies the majority of patients received phenothiazines for the treatment of insomnia, vomiting, and anxiety, and not for the therapy of psychiatric disorders, so that medications were probably not taken at the schedule and dosage usually administered to psychotic subjects. In one study in which the risk of abnormalities after in utero exposure was similar to that of unexposed children (Milkovich and Van der Berg, 1976), a re-examination of findings, using a longer follow-up time, demonstrated a trend toward an increased rate of malformations in infants exposed in utero to phenothiazines in weeks 4 to 10 of pregnancy (Edlund and Craig, 1984). Another study revealed an association between gestational phenothiazine exposure (including exposure during the first trimester) and an enhanced rate of birth defects (Rumeau-Rouquette et al., 1977). More specifically, this study, correlating the different outcomes with the chemical structure of phenothiazines used during the pregnancy, has provided evidence that phenothiazines with three carbon aliphatic side chains (e.g., chlorpromazine) were associated with a higher rate of malformations, whereas those with two carbon side chains were not. A large prospective study that analyzed data published between 1963 and 1995 on the effects of prenatal exposure to neuroleptics reported that gestational use of low-potency neuroleptics may confer a significant, albeit small, increase in the likelihood of poor outcome (Altshuler et al., 1996). Unfortunately, the nature of this meta-analysis excluded the possibility to assess differential risks associated with individual phenothiazines (Pinkofsky et al., 1997). Few studies have investigated fetal outcome for pregnant women treated with high-potency neuroleptics, and most data refer to the effect of prenatal haloperidol. Although two early case reports describing limb malformations raised concerns regarding first-trimester exposure to haloperidol (McCullar and Heggeness, 1975; Dieulungard et al., 1996), several studies failed to demonstrate an increased teratogenic risk with this drug (Van Waes and Van de Velde, 1969; Hanson and Oakley, 1975). Nevertheless, similar to low-potency antipsychotics, in the large majority of these studies

women were given haloperidol in association with other medications, thus not allowing definite conclusions.

In recent years, increasing attention has been given to the more subtle, nonstructural alterations produced by drugs given prenatally. Such changes involving motor ability, emotionality, and learning and memory capability constitute a sensitive tool for detecting subtle damage to the functioning of the central nervous system induced by exposure to medications at sensitive phases and at dose levels frequently below those commonly associated with manifest signs of neurotoxicity (Cuomo, 1987). These alterations in behavior seem to be partly due to drug-induced changes in the developmental pattern of specific neurotransmitter systems.

Most studies examining the influence of prenatal antipsychotic exposure have focused on various aspects of the dopaminergic system. In the majority of these investigations, haloperidol has been used as prototype of this class of drugs. In utero haloperidol exposure has been found to decrease cell proliferation in the forebrain (Blackhouse et al., 1982; Patel and Lewis, 1988) and to affect the expression of DNA polymerase in the mesencephalon and forebrain (Castro et al., 1990). Additionally, gestational haloperidol exposure induces a reduction of nerve growth factor receptors and mRNA in neonate rat forebrain (Alberch et al., 1991), suggesting that prenatal haloperidol exposure may have a critical impact on forebrain development. This assumption has been confirmed by electrophysiological investigations demonstrating that in 2-week-old pups prenatal haloperidol caused a significant decline in the number of spontaneously active midbrain dopamine neurons. However, whether the decrease in the number of active cells may result from a physical loss rather than from a functional change in the threshold of spontaneous activity is still uncertain (Zhang et al., 1996). Prenatal dopamine receptor occupancy was demonstrated to be a critical factor in controlling the development of forebrain target cells through selective changes in the expression of plasticity-related genes, whereas the expression of other genes, including several proto-oncogenes, was unaffected (Castro et al., 1994). Moreover, the widespread distribution of *c-fos* gene expression in the fetal rat brain following dopamine D_1 receptor stimulation is in contrast to the response of *c-fos* occurring in adult rats (Shearman et al., 1997), when D_1 receptor activation induces *c-fos* gene expression after depletion of dopamine. Denervating lesions of dopaminergic projections reduced D_1 postsynaptic receptor expression in the immature nervous system and up-regulated D_1 receptors in mature rodents (LaHoste and Marshall, 1994). This indicates that removal of dopaminergic innervation or receptor blockade in immature brain results in a paradoxical change, rather than in compensatory overexpression of dopamine receptors, as observed in adult rats.

Prenatal haloperidol treatment did not alter levels of dopamine and its metabolites in the basal ganglia of 1- to 58-day-old rats (Rosengarten et al., 1983; Williams et al., 1992). However, gestational exposure to haloperidol has been shown to reduce the number of postsynaptic dopamine receptors (Rosengarten and Friedhoff, 1979; Miller and Friedhoff, 1986; Scalzo et al., 1989), although other reports did not confirm these findings (Madsen et al., 1981; Moon, 1984; Schmidt and Lee, 1991). Moreover, depending on the timing of exposure, developmental treatment with haloperidol can affect the response of rat offspring to pharmacological challenges to the dopaminergic system (Rosengarten and Friedhoff, 1979; Spear et al., 1980; Cuomo et al., 1985; Scalzo and Spear, 1985). In particular, prolonged prenatal exposure of rats to haloperidol has been found to significantly influence their behavioral responsiveness to a dopamine receptor agonist such as apomorphine at 60 days of age. The intensity of stereotyped behaviors as well as the effects on locomotor activity elicited by apomorphine in haloperidol-pretreated animals have been shown to be markedly attenuated when compared with controls (Rosengarten and Friedhoff, 1979; Cuomo et al., 1985). These data, indicating a behavioral subsensitivity of the dopaminergic system of haloperidol-exposed rats to pharmacological stimulation, parallel neurochemical results showing a decrease in [^{3}H]spiroperidol binding in the striatum of rats born to mothers treated with haloperidol during gestation (Rosengarten and Friedhoff, 1979). On the other hand, the prolonged administration of haloperidol during the first 3 weeks of postnatal life has been reported to produce, in 60-day-old rats, an opposite response pattern (behavioral supersensitivity to apomorphine) which again correlates with neurochemical data (increased [^{3}H]spiroperidol binding in the striatum) (Rosengarten and Friedhoff, 1979). Furthermore, a challenge dose of haloperidol induces smaller increases in dopamine turnover in adult rats treated with this neuroleptic during early postnatal life (Cuomo et al., 1981). Although increased central dopamine receptor sensitivity to apomorphine as well as an attenuated response to a challenge of haloperidol on dopamine turnover after prolonged haloperidol treatment also occur in adult rats, there is no evidence that these changes persist up to 40 days after the last administration of this neuroleptic agent (Cuomo et al., 1983b). These findings suggest that the particular period of developmental administration of haloperidol plays a critical role in causing enduring neurofunctional changes (Cuomo et al., 1983b) and that compensatory mechanisms occurring in response to a prolonged treatment during development are markedly different from those occurring during adulthood.

Additional studies have shown that prolonged postnatal exposure to haloperidol alters the ultrasonic emission elicited by the removal of rat pups from their nest (Cagiano et al., 1986). This response is a reliable indi-

cator of emotional reactivity during development. In particular, neonatal administration of this neuroleptic agent produced a significant decrease in the rate of calling, an increase in the duration of calls, and a decrease in the minimum and maximum frequency of calls. There is evidence that dopamine plays an important role in the regulation of sexual behavior in rats (Gessa and Tagliamonte, 1975), and dopaminergic mechanisms are thought to underlie sexual dysfunctions produced by the administration of some neuroleptics (Buffum, 1982; Segraves, 1982). In this regard, Hull et al. (1984) have shown that the prolonged administration of haloperidol to pregnant rats, at a relatively high dose (2.5 mg/kg), impairs the sexual behavior of male offspring. Indeed, haloperidol-exposed animals had significantly fewer ejaculations than controls. Since ultrasonic calls emitted by male rats during mating activity seem to be a sensitive indicator of their sexual motivation (Barfield et al., 1979), the aim of other studies was to investigate the influence of prenatal or early postnatal exposure to a low dose of haloperidol (0.5 mg/kg), which itself does not affect sexual behavior in the offspring, on both preejaculatory and postejaculatory ultrasonic vocalizations. The results showed that the latency of emission of the first precopulatory 50-kHz call was not influenced by the early postnatal haloperidol treatment. Conversely, the period of the 22-kHz call emission was shorter in haloperidol-treated animals than in controls (Cuomo et al., 1991). The comparison of the results of this study with those of previous experiments (Cagiano et al., 1988) further confirms that the behavioral consequences of developmental treatments with this dopamine antagonist are critically dependent upon the period of administration. In fact, the latency of emission of the first precopulatory 50-kHz ultrasound as well as the duration of the period of the 22-kHz postejaculatory call emission were significantly increased by prenatal exposure to haloperidol (Cagiano et al., 1988; Cuomo et al., 1990). Since it has been shown that D_2 dopamine receptors are involved in the emission of 22-kHz postejaculatory calls (Cagiano et al., 1989), the selective alterations in this ultrasonic parameter produced by prenatal and neonatal treatment with haloperidol may be due to interactions with the development of this receptor subtype. Finally, the finding that developmental administration of haloperidol to two inbred strains of mice (C57 BL/6J and DBA/2J), who display an opposite behavioral reactivity to stimulation of dopamine receptors (Sansone et al., 1981), caused distinct behavioral changes in their offspring (Cuomo et al., 1984) and also suggests that pharmacogenetic determinants play a role in the behavioral consequences of developmental exposure to this neuroleptic.

In contrast to the abundance of animal studies, human studies focusing on the potential neurobehavioral sequelae of prenatal exposure to typical antipsychotics are very limited. In the absence of a continuous follow-up, it is not possible to evaluate the neurobehavioral effects in children born to mothers treated with antipsychotics while pregnant. However, after a follow-up to the age of 5 years, two studies by Edlund and Craig (1984) and Kris (1965) did not report significant differences in behavioral and intellectual functioning in children with and without histories of prenatal exposure to typical neuroleptics. Moreover, in a case-control study, Stika et al. (1990) failed to document any difference between infants receiving and not receiving medications when evaluating school behavior and proficiency of 68 children gestationally exposed to typical neuroleptics. Thus, the limited data in humans sharply diverge from those provided by animal studies; in animals gestational exposure to antipsychotics has been shown to cause a variety of biochemical and behavioral abnormalities whose relevance to humans remains unclear.

2. Atypical Antipsychotics. Atypical antipsychotics exhibit a lower affinity for D_2 dopamine receptors, and in addition to α-adrenoceptor blockade, these compounds have some affinity for 5-HT_{2A} serotonin receptors (Leysen et al., 1994). Compared with the traditional agents, all second-generation antipsychotics have a higher ratio of 5-HT_2 to D_2 receptor blockade, so that, in addition to the term atypical agents, they might be also designated as serotonin/dopamine antagonists. This profile of moderate affinities for several central receptor types (also including muscarinic cholinergic and H_1-histamine receptors) may account for their pharmacological effects. Clozapine also possesses a modest selectivity for dopamine D_4 receptors over other dopamine receptor subtypes (Baldessarini and Tarazi, 2001); however, although D_4 dopamine receptors have been suggested to mediate the clinical effects of atypical antipsychotics, selective D_4 or mixed D_4/5-HT_{2A} antagonists failed to be effective in the treatment of psychosis (Baldessarini et al., 1997; Truffinet et al., 1999). Unlike traditional neuroleptics, atypical antipsychotics, with the exception of risperidone, have not been associated with increased serum prolactin and therefore are less likely to inhibit ovulation and female fertility. A change from conventional oral or depot antipsychotics to atypical drugs may consequently result in unwanted pregnancies, which are of particular concern in women with chronic psychotic illnesses (Gregoire and Pearson, 2002). Although their use is steadily increasing, information about gestational effects of atypical agents is still very limited.

Clozapine's structure comprises an aromatic moiety (a tricyclic dibenzodiazepine) and an aliphatic moiety, which is similar to phenothiazines. Animal investigations, where doses much higher than the maximum recommended dose in humans were used, failed to demonstrate any increased incidence of malformations. There are still few reports on human pregnancies (20 cases) in which exposure to clozapine has occurred (Lieberman and Safferman, 1992; Waldman and Safferman, 1993; Barnas et al., 1994; Stoner et al., 1997). Two of these

reports have described the use of clozapine throughout the first trimester. In none of the pregnancies have either the women or their infants experienced adverse effects. On the other hand, Dev and Krupp (1995) have documented cases of 61 infants gestationally exposed to clozapine. Although 51 of the children were healthy at birth, five neonates suffered from transient perinatal syndromes, and five others displayed congenital malformations. However, in the latter cases, women were given medications other than clozapine, which may have contributed to fetal damage.

Risperidone, a benzisoxazole derivative, has prominent antiserotoninergic (5-HT_2) as well as antidopaminergic (D_2) and antihistaminergic (H_1) activities. Although risperidone and clozapine share some receptor affinities, risperidone is a much more potent antidopaminergic agent and causes extrapyramidal side effects as well as hyperprolactinemia (at daily dose of 6 mg or more) (Baldessarini and Tarazi, 2001). Animal studies have shown that risperidone does not induce direct reproductive toxicity, although some prolactin- and central nervous system-mediated effects have been reported (Association of the British Pharmaceutical Industry, 1999-2000). In a recent report describing two cases of risperidone treatment before and throughout pregnancy, no complications were observed (Ratnayake and Libretto, 2002). This is in agreement with the findings of a postmarketing study of 7684 patients who were prescribed risperidone (Mackay et al., 1998). Among nine pregnant women treated with risperidone there were seven live births and three therapeutic terminations; no abnormalities were reported among the seven live children exposed in utero to the drug.

Olanzapine has a thienobenzodiazepinyl structure. In addition to dopamine receptors, olanzapine interacts with several other classes of receptors with varying affinities (α_1- and α_2-adrenergic, serotonin 5-HT_{2A} and 5-HT_{2C}, muscarinic cholinergic, histamine H_1, and others) (Baldessarini and Tarazi, 2001). Olanzapine has a greater affinity for 5-HT than for dopamine receptors, which accounts for its greater efficacy (even in patients with refractory schizophrenia), and for a much lower incidence of extrapyramidal side effects. Information on the use of olanzapine in pregnancy is limited to reproduction studies in animals. No evidence of teratogenicity was observed in rats and rabbits at doses equivalent to 9 and 30 times the maximum recommended human daily doses, respectively (Hagopian et al., 1987). Only a few case reports dealing with olanzapine treatment during pregnancy are present in the literature. One case ended with a therapeutic abortion performed at the patient's request, and no fetal abnormalities were observed (Dickson and Dawson, 1998), whereas in two others no adverse effects were found in the newborns (Kirchheiner et al., 2000; Littrell et al., 2000). Finally, a study in which 23 pregnancies were followed suggested a favorable risk-to-benefit ratio for the fetus and infant following olanzapine exposure, since spontaneous abortion, prematurity, or major malformation in offspring did not occur (Goldstein et al., 2000). No case reports or other studies were found on administration of sertindole, ziprasidone, and quetiapine during pregnancy.

Animal studies indicate that developmental exposure to an atypical noncataleptogenic neuroleptic, such as clozapine, produces neurochemical and behavioral changes that markedly differ from those elicited by a typical cataleptogenic neuroleptic, such as haloperidol. In particular, early postnatal exposure to clozapine does not modify either apomorphine-induced stereotypes or the effect of apomorphine of locomotor activity in adult rats. Moreover, neurochemical data have indicated that even if an acute challenge dose of clozapine (10 mg/kg) induces a certain degree of tolerance, a single dose of 20 mg/kg of this neuroleptic was still able to increase striatal homovanillic acid levels in adult rats which were treated with clozapine during early postnatal life (Cuomo et al., 1983a). These findings also differ from those obtained with cataleptogenic neuroleptics. On the other hand, early postnatal exposure to clozapine significantly impairs the acquisition of a differential-reinforcement of low-rate-of-responding (DRL) 15-s schedule, and in this regard, the behavioral changes are similar to those caused by haloperidol. As impairment of DRL 15-s performance by the atypical antipsychotic flupentixol was associated with a significant decrease of the noradrenergic metabolite MOPEG (3-methoxy-4-hydroxyphenylglycol) in rat forebrain (Nielsen, 1977), the similar effects of clozapine may be related to its ability of interfering with the developing noradrenergic system (Burki et al., 1974).

Similar to typical neuroleptics, in particular haloperidol (Archer and Fredrikson, 1992; Archer, 1993), atypical antipsychotics also exert long-lasting detrimental effects on cognitive function after administration during vulnerable phases of brain development. In addition to the limited data available for clozapine, recent results have reported the effects of prenatal exposure to other atypical neuroleptics, such as olanzapine, quetiapine, and risperidone, on cognitive functions of adult rats (Table 2) (Rosengarten and Quartermain, 2002). These results have revealed a disruptive action exerted by gestational quetiapine and risperidone (treatments on spatial learning), whereas only the latter significantly

TABLE 2
Effects of prenatal treatment with typical and atypical neuroleptics on cognitive functions in rats

Neuroleptics	Spatial	
	Learning	Memory
Haloperidol	↓	↓
Quetiapine	↓	NE
Risperidone	↓	↓
Olanzapine	NE	NE

NE, no effect; ↓, decreased effect.
Adapted from Rosengarten and Quartermain (2002).

impairs the retention process. In contrast, maternally administered olanzapine does not interfere with either learning or retention. Such findings indicate that although quetiapine and risperidone are similar to typical neuroleptics in affecting acquisition of spatial learning, only risperidone resembles haloperidol in disrupting the retention process in rodents. Interestingly, the effects of olanzapine are different from both haloperidol and risperidone with regard to learning and memory, but parallel to those of quetiapine with regard to retention but not learning function.

There is only very limited information on the possible mechanisms underlying such different patterns of responses. It has been suggested that antipsychotics with low affinity for dopamine and 5-HT receptors may be readily displaced by the endogenous neurotransmitters and thus possess a reduced potential for cognitive disruption in the developing brain (Rosengarten and Quartermain, 2002). However, the different effects observed cannot be fully explained on the basis of the different in vitro and in vivo profile of receptor affinities displayed by the neuroleptics tested. For instance, quetiapine has a receptor occupancy profile for D_2 dopamine and 5-HT_2 serotonin receptors significantly lower than olanzapine; however, in contrast with olanzapine, it adversely affects learning. Thus, although the biochemical mechanisms underlying the behavioral alterations caused by prenatal administration of olanzapine, quetiapine, and risperidone remain unclear, these limited results represent a relevant step in the process of identification of potential neurofunctional sequelae of prenatal exposure to atypical antipsychotics. Unfortunately, to date, no studies are available on the potential long-term behavioral sequelae in the offspring of women exposed to atypical antipsychotics during pregnancy.

B. Antiepileptic Drugs

It is estimated that 0.4 to 0.8% of pregnant women have epilepsy, and many of these women need to continue taking medication to control seizure during pregnancy (Stoler, 2001). Maternal seizures during pregnancy may themselves pose a risk for the fetus (Minkhoff et al., 1985; Gaily et al., 1988), and now there is sufficient evidence indicating that exposure to anticonvulsant drugs causes developmental toxicity. In a recent study, 1 in 251 pregnant women was found to take antiepileptic drugs, particularly phenytoin, carbamazepine, valproic acid, and phenobarbital (Holmes et al., 2001). These drugs have been found to cause major malformations, microcephaly, growth retardation, and distinctive minor abnormalities of the face and fingers in infants following prenatal exposure (Hanson and Smith, 1975; Seip, 1976; Winter et al., 1987; Jones et al., 1989). In some cases, such as with phenobarbital and phenytoin, extensive animal studies have documented major developmental effects, as well as more subtle neurofunctional and behavioral abnormalities (Hansen and Holson, 1998). On the other hand, long-term follow-up of children exposed to antiepileptic drugs in utero has been more limited, so relatively little is known about the subsequent neurological and cognitive development of these children (Adab et al., 2001). Yet this may be an area of concern, as major congenital abnormalities may simply represent the tip of the teratogenic iceberg (Rosser and Wilson, 1999). Furthermore, in humans, the situation may be often complicated by polytherapy since interactions among anticonvulsant drugs are common and may lead to an enhancement of teratogenic and other developmental effects.

1. Valproic Acid. Valproic acid (dipropylacetic acid) is a short-chained fatty acid widely used in humans as an anticonvulsant and a mood stabilizer (Johannessen, 2000). Its anticonvulsant activities were discovered serendipitously in the 1960s during its use as a solvent for other potentially antiseizure compounds, and it was approved for use in the United States in 1978. Although valproic acid is being used as an effective drug to control generalized and partial seizures, its mechanism of action has not yet been elucidated. The most widely accepted hypothesis is that valproic acid acts by increasing the concentration of the inhibitory neurotransmitter GABA, possibly as a consequence of its ability to stimulate GABA synthesis and inhibit its degradation (Johannessen, 2000). GABA is degraded by GABA transaminase to succinate semialdehyde, which is converted to succinate by succinate dehydrogenase. Both enzymes, but particularly the latter, are inhibited by valproic acid (Johannessen, 2000). Valproic acid also acts at the voltage-dependent sodium channel, inhibiting high-frequency firing of neurons (Johannessen, 2000).

Valproic acid is an animal and human teratogen (Cotariu and Zaidman, 1991). Neural, renal, cardiac, urogenital, and musculoskeletal abnormalities have been found in rabbits (Petrere et al., 1986), rodents (Kao et al., 1981; Ong et al., 1983), and nonhuman primates (Mast et al., 1986). In humans, in utero exposure to valproic acid has been associated with neural, craniofacial, cardiovascular, and musculoskeletal defects (Table 3) (Jager-Roman et al., 1986; Winter, 1987; Kozma, 2001). The developing nervous system appears to be particularly sensitive to the developmental toxicity of valproic acid, as neural tube defects, specifically spina bifida, occur at a very high rate upon in utero exposure to this compound (Bjerkedal et al., 1982; Lindhout and Schmidt, 1986). Neural tube defects are also seen in mice (Paulson et al., 1985), where strain differences in susceptibility suggest an underlying genetic predisposition (Finnell et al., 1988; Faiella et al., 2000).

Because of its severe teratogenic effects, most research has focused on the mechanisms underlying major malformations induced by valproic acid (Finnell et al., 2002). Faiella et al. (2000) noted that many valproic acid-induced malformations in mice resulted from homeotic transformations of the vertebral column and

TABLE 3
Characteristics of the fetal valproate syndrome

Malformation	Incidence	Percentage (n = 67–70)
Craniofacial abnormalities	Small/broad nose	57
	Small/abnormal ears	46
	Long/flat philtrum	43
	Thin vermillion border	37
	Epicanthal folds	31
	Hypertelorism	27
	High/broad forehead	26
	Micro/retrognathia	26
	Bifrontal narrowing	17
Organ malformations	Musculoskeletal system	63
	Skin and appendages	29
	Cardiac abnormalities	26
	Genital abnormalities	16
	Brain abnormalities	10
Evolution	Developmental deficits	20
	Growth retardation	15
	Hypotonia	10
	Mental retardation	10

Adapted from Kozma (2001).

were similar to those observed in mice treated with retinoic acid. As retinoic acid alters the expression of homeobox genes (Morriss-Kay and Ward, 1999), the effect of valproic acid on Hox expression was examined in human embryonal carcinoma cells. At therapeutically relevant concentrations, valproic acid was found to alter the expression of certain homeobox genes (Faiella et al., 2000), leading the authors to propose that valproic acid teratogenicity may be, at least in part, mediated through changes in Hox gene expression.

The ability of valproic acid to reduce the proliferation of C6 glioma cells by blocking cells in the G_0/G_1 phase (Martin and Regan, 1991; Bacon et al., 2002), together with the fact that alterations of normal proliferative rate of the tissues involved with neural tube closure may result in an embryo with a neural tube defect, have led to the hypothesis that antiproliferative effects of valproic acid may be at the basis of its teratogenicity (Finnell et al., 2002). Earlier hypotheses on the developmental toxicity of valproic acid included the suggestion that this compound may cause zinc deficiency; however, in vitro work has suggested that this is not the mechanism of embryotoxicity (Coakley and Brown, 1986). A deficiency in folic acid has also been suggested as a potential mechanism; however, in vivo supplementation studies with the folate metabolite folinic acid gave contradictory results (Hansen and Grafton, 1991; Wegner and Nau, 1991; Elzamar et al., 1992). Recently, however, changes in the expression of the folate pathway genes including the folbp-1 and -2 genes and the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene were found in embryos harvested from valproic acid-exposed dams (Finnell et al., 1997). Additional changes were found in the expression of genes involved in cell cycle and apoptosis, such as p53 and bcl-2, as well as in growth factor genes (nerve growth factor, brain-derived-neurotrophic factor) (Wlodarczyk et al., 1996).

Recently, valproic acid has been found to be an effective inhibitor of histone deacetylase, with an IC_{50} of 0.4 mM, well within its therapeutic range (Göttlicher et al., 2001; Phiel et al., 2001). Histone acetylation has been shown to be an important regulatory mechanism for controlling transcription in ~2% of transcribed genes (Van Lint et al., 1996); histone deacetylase is thus involved in the repression of gene expression and plays an important role in embryonic development. Interestingly, a known inhibitor of this enzyme, trichostatin A, causes developmental effects similar to those of valproic acid in *Xenopus* embryos (Phiel et al., 2001). Furthermore, inhibition of histone deacetylase can also prevent proliferation of numerous cell types, and such an effect may be at the basis of the previously discussed inhibition of glioma cell proliferation by valproic acid (Martin and Regan, 1991). This inhibition of histone deacetylase by valproic acid has been suggested to contribute to its anticonvulsant activity (Phiel et al., 2001), although this appears to be unlikely, as analogs of valproic acid have been found that have antiepileptic activity but are not teratogenic (Nau et al., 1991; Göttlicher et al., 2001).

Unlike phenobarbital and phenytoin, limited information exists on the effects of valproic acid on the developing brain at doses that do not induce severe teratogenesis (Hansen and Holson, 1998). Early postnatal exposure was found to decrease brain weight in mice (Thurston et al., 1981), whereas gestational exposure in rats was reported to cause membrane order abnormalities (Vorhees et al., 1991). Gestational exposure of rodents to valproic acid has also been reported to cause behavioral changes in the offspring, such as deficits in spatial learning tasks (Vorhees, 1987a) and in spontaneous activity (Sobrian and Nandedkar, 1986; Vorhees, 1987a), and alterations in sensitivity to pentylenetetrazole-induced seizures (Sobrian and Nandedkar, 1986; Pizzi et al., 1988).

In humans, limited follow-up studies on surviving patients have documented brain abnormalities, developmental delays, and mental retardation in addition to craniofacial, musculoskeletal, and cardiovascular defects (Table 3) (Kozma, 2001). Hattig et al. (1987) reported a higher incidence of cognitive impairment in children exposed to valproate; developmental delays, hyperactivity, learning difficulties, and other behavioral problems were also observed (Moore et al., 2000b). It has been suggested that valproate may be more toxic to the developing brain than other anticonvulsants (Moore et al., 2000b). Based on the high percentage (30%) of children exposed to valproic acid monotherapy in utero who had additional educational needs, Adab et al. (2001) also suggested that "valproate carries particular risks to learning and development of children" and that "well identified risks of neural tube defects and a fetal valproate syndrome may be the tip of the iceberg" (Table 4). An association of prenatal exposure to valproic acid and autism or autistic-type behaviors has also been sug-

TABLE 4
Additional educational needs of children exposed in utero to antiepileptic drugs

	Mainstream School	Additional Needs	Percentage
No drugs	156	20	11
Valproic acid	39	17	30[a]
Carbamazepine	61	2	3
Other	29	2	6

[a] $P < 0.05$.
Adapted from Adab et al. (2001).

gested (Christianson et al., 1994; Moore et al., 2000b). Interestingly, in utero exposure of rats to valproic acid was found to reproduce the cerebellar anomalies associated with autism (Ingram et al., 2000).

Despite the limited but increasing evidence that prenatal exposure to valproic acid may be associated with neurofunctional abnormalities in the offspring, very little mechanistic research has been carried out. In one of the few studies, using an in vitro system of organotypic cultures of rat hippocampus, Fennrich et al. (1998) found that valproic acid, at concentrations of 0.5 to 5 mM, hampered the regular formation of the pyramidal cell layer. They attributed such effect to a specific and selective action of valproic acid on radial astrocytes that would lead to alterations in neuronal network formation.

As shown by this brief review of the literature, knowledge of the possible mechanisms of valproic acid teratogenicity and developmental toxicity is still incomplete. Histone deacetylase appears to be a novel credible target to explain at least some teratogenic effects of valproic acid. However, mechanisms of more subtle neurofunctional effects of in utero exposure to valproic acid have not been considered in any detail. In particular, hypotheses that may link its therapeutic effects with its developmental toxicity have only recently been investigated. For example, GABA agonists, when given during the brain growth spurt (early postnatal days in rodents, equivalent to the third trimester of pregnancy in humans), have been shown to cause neuronal apoptotic death (Ikonomidou et al., 2001). In a preliminary study, administration of valproic acid to neonatal rats, at doses below the ED_{50} for anticonvulsant action, has been shown to induce widespread apoptotic neurodegeneration in several brain areas (Bittigau et al., 2000). Coupled to inhibition of histone deacetylase, which can also lead to apoptotic cell death (Marks et al., 2000), this would potentially lead to severe neurofunctional abnormalities.

2. Phenytoin. Phenytoin (diphenylhydantoin; Dilantin, Warner-Lambert Co., Morris Plains, NJ) was first synthesized in 1908, but its anticonvulsant activity was not discovered until 1938. It is effective against all types of partial and tonic-clonic seizures, but not against absence seizures. Its mechanism of action appears to involve an interaction with sodium channels; phenytoin limits the repetitive firing of action potentials evoked by sustained depolarization, by slowing the rate of recovery of voltage-activated sodium channels from inactivation (McNamara, 2001). At higher than therapeutic concentrations, phenytoin can also enhance the responses to GABA (McNamara, 2001). Whether prolonged exposure to high levels of phenytoin can lead to cerebellar damage in adult animals is still controversial (Dam and Nielsen, 1970; Volk et al., 1986).

There is ample evidence that phenytoin is a developmental toxicant in animals and humans (Hanson, 1976; Hansen, 1991). The fetal hydantoin syndrome in humans is characterized by facial dysmorphologies (shallow philtrum, thin lip, broad nasal bridge, short nose, facial hirsutism), hypoplasia of distal phalanges, growth retardation, and occasional skeletal, cardiac, or genitourinary anomalies (Hanson, 1976; Kelly et al., 1984; Van Dyke et al., 1988; Moore et al., 2000b). Abnormal development has also been observed in rodents (Finnell and Danski, 1991). In mice, growth retardation, skeletal defects, hydrocephalus, ectrodactyly, and orofacial clefting have been reported (Harbison and Becker, 1969; Finnell and Chernoff, 1984). Animal studies have also shown that gestational and neonatal phenytoin treatment causes a reduction in brain weight (Tachibana et al., 1996; Hatta et al., 1999).

A large number of studies have shown that phenytoin can be neurobehaviorally teratogenic in animals at doses below those producing malformations (Table 5) (Elmazar and Sullivan, 1981; Vorhees, 1987b; Vorhees and Minck, 1989; Minck et al., 1991; Pizzi and Jersey, 1992). A broad range of behavioral deficits has been found in these animals, most notably a substantial difficulty with spatial learning tasks, including spontaneous alternation, the Biel or Cincinnati water mazes, and the Morris and radial eight-arm mazes (Vorhees and Minck, 1989; Weisenburger et al., 1990; McCartney et al., 1999; Schilling et al., 1999). Activity changes (hyperactivity) are also prominent in rats after gestational phenytoin exposure (Vorhees, 1987b; Vorhees and Minck, 1989; Weisenburger et al., 1990; Tachibana et al., 1996; McCartney et al., 1999; Schilling et al., 1999). A striking spontaneous circling behavior has also been observed in some, but not all, animals, which has been suggested to be due to a midear problem, although this has not been confirmed (Hansen and Holson, 1998).

TABLE 5
Behavioral teratogenicity of perinatal phenytoin and phenobarbital in rats

Effect	Phenytoin	Phenobarbital
Spatial learning	↓	↓
Activity	↑	?
Motor coordination	↓	↓
Operant learning	NA	↓
Conditioned avoidance	NE	↓

NA, no information available; NE, no effect.
Adapted from Hansen and Holson (1998).

Overall, these data suggest that phenytoin can cause abnormalities within the auditory-vestibular cerebellar system and likely the hippocampus (Hansen and Holson, 1998). Cerebellar damage has been found in mice after administration of phenytoin during the neonatal period (Ohmori et al., 1992, 1997), but no information exists on hippocampal effects. In humans, phenytoin has been shown to cause microcephaly (Hanson, 1976; Adams et al., 1990; Dessens et al., 2000), as well as learning disabilities and decreased IQ scores (Hanson, 1976; Van Dyke et al., 1988; Van Overloop et al., 1992; Scolnik et al., 1994; Dessens et al., 2000).

Studies carried out to investigate potential mechanisms of phenytoin teratogenicity and developmental neurotoxicity have yielded only minor results (Hansen, 1991). Antagonism of folate has been suggested to play a role in embryotoxicity, but, as in the case of valproate, supplementation with exogenous folate has provided contrasting results (Marsh and Fraser, 1973; Mercier-Parot and Tuchmann-Duplessis, 1974). An involvement of glucocorticoids in phenytoin-induced normal palatal development has also been suggested, but the findings are inconclusive (Hansen et al., 1988).

Studies on the mechanisms of phenytoin developmental neurotoxicity have focused on the cerebellum. Neonatal exposure of mice (corresponding to the third trimester of pregnancy in humans) leads to cerebellar damage, characterized by apoptotic death and delayed migration of granule cells and altered development of Purkinje cells (Ohmori et al., 1999). Phenytoin has been shown to induce apoptotic cell death of cultured cerebellar granule cells in vitro (Yan et al., 1995) and degeneration of Purkinje cells in vitro (Blank et al., 1982). Limited information exists on specific effects (and mechanisms) of phenytoin in areas such as the hippocampus or the cerebral cortex, where the damage may be associated with the cognitive deficits observed in both animals and humans. In an in vitro study, phenytoin was found to be toxic to cerebral cortical cell cultures following prolonged exposure (Neale et al., 1985). A recent interesting finding has been reported by Ikonomidou et al. (2000), who found that a number of drugs that block sodium channels, including phenytoin, cause a dose-dependent increase in apoptotic neuronal cell death in the developing brain, affecting the hippocampus, cortical areas, the amygdala, and the thalamus. Such preliminary results appear promising, as they may offer new insights on the mechanism(s) underlying the developmental neurotoxicity of phenytoin.

3. Phenobarbital. Phenobarbital is one of the two barbiturates used for therapy of the epilepsies; the other is primidone, which is converted in vivo to phenobarbital and phenylethylmalonamide. Phenobarbital was the first effective organic seizure agent, has been used for over 90 years, and remains one of the most effective and widely used antiepileptic drugs. The mechanism by which phenobarbital inhibits seizures involves mostly potentiation of synaptic inhibition through an action on $GABA_A$ receptors.

There is evidence that phenobarbital is a developmental toxicant and neurotoxicant. Animal studies have shown that both prenatal and neonatal exposure of rats can reduce brain weight (Schain and Watanabe, 1975; Diaz et al., 1977). A series of detailed studies on the effect of perinatal administration of phenobarbital in the developing brain has been carried out by Yanai and coworkers. Such exposures cause Purkinje cell death, reduced cerebellar weight, reduction in the number of granule cells in the cerebellum (Yanai and Iser, 1981; Fishman et al., 1983; Yanai and Waknin, 1985), and reduction of both pyramidal and granule cell number in the hippocampus (Yanai et al., 1979; Bergman et al., 1982). Neurochemical studies indicated limited effects on norepinephrine, dopamine, and GABA neurotransmitter systems (Middaugh et al., 1981; Pick et al., 1993) and a more robust effect on cholinergic neurotransmission in the hippocampus (Rogel-Fuchs et al., 1992; Abu-Roumi et al., 1996).

Results of behavioral studies are overall consistent with the morphological and neurochemical changes. Perinatal exposure to phenobarbital in rats and mice causes decrements in spatial learning task including the radial eight-arm maze, the Morris water maze, and spontaneous alternation (Table 5) (Kleinberger and Yanai, 1985; Pick and Yanai, 1985; Rogel-Fuchs et al., 1992). Limited data exist on the potential effects of phenobarbital on motor activity, which may be expected given the cerebellar damage observed (Hansen and Holson, 1998).

Although phenobarbital is clearly a developmental neurotoxicant, little evidence exists on its embryotoxicity and teratogenicity in experimental animals. Although an increase of cleft palate was reported (Sullivan and McElhatton, 1975), phenobarbital appears to be less embryotoxic than other anticonvulsants in animal models (Hansen and Holson, 1998). In humans, teratogenic effects of phenobarbital have been reported, and the facial dysmorphia, growth retardation, and other minor malformations resemble those found with other anticonvulsants (Seip, 1976; Holmes et al., 2001). As phenobarbital appears to cause significant central nervous system abnormalities in laboratory animals, even in the absence of observable morphological anomalies at birth, research has focused on behavioral abnormalities following prenatal exposure. Van der Pol et al. (1991) reported that cognitive development of children was significantly impaired. Similarly, children exposed prenatally to phenobarbital scored significantly lower on the Bayley Mental Developmental Index (Thorp et al., 1999). Cognitive effects, with IQ deficiency, were also reported in children who received phenobarbital as toddlers for febrile seizures (Sulzbacher et al., 1999). A study of adult males exposed in utero to phenobarbital found significantly lower verbal intelligence scores, particularly when expo-

sure occurred also during the third trimester of pregnancy (Table 6) (Reinisch et al., 1995).

Little is known of the possible mechanisms underlying the developmental neurotoxicity of phenobarbital. Recently, however, it was found that administration of therapeutic doses of phenobarbital to neonatal rats causes a wave of apoptotic neurodegeneration, which is ascribed to the GABA-mimetic action of this compound (Bittigau et al., 1999, 2000).

4. Carbamazepine. Carbamazepine is a iminostilbene derivative, structurally similar to the tricyclic antidepressants, first introduced in the 1960s for the treatment of partial and tonic-clonic seizures (Albani et al., 1995). The antiseizure effects are thought to be due to its ability to bind to sodium channels when they are in the inactivated state, slowing the spread of reactivation and thus reducing the neuron's capacity of high frequency firing, although interactions with various neurotransmitter systems have also been reported (Albani et al., 1995).

Carbamazepine has been found to be teratogenic in humans. The pattern of malformations in children whose mothers were treated with carbamazepine during pregnancy include facial dysmorphic features (short nose, long philtrum, hypertelorism), microcephaly, growth retardation, and fingernail hypoplasia (Hiilesmaa et al., 1981; Jones et al., 1989; Samren et al., 1997). A recent study of 210 pregnancies suggests a 2-fold increase in the rate of congenital anomalies due to carbamazepine therapy (Diav-Citrin et al., 2001). Similarly, in a meta-analysis of 1255 cases of exposure to carbamazepine during pregnancy, an increased rate of congenital anomalies, mainly neural tube defects, cardiovascular and urinary tract anomalies, and cleft palate, was found (Matalon et al., 2002). Mild mental retardation has also been reported (Ornoy and Cohen, 1996), but the need for additional education in children born to mothers receiving carbamazepine was low compared with those exposed to valproic acid (3.2% versus 30%) (Adab et al., 2001) (Table 4). Similarly, no neurologic differences from controls were found in a group of 6- to 13-year-old children exposed in utero to carbamazepine (Van der Pol et al., 1991), and Scolnik et al. (1994) found no impairment in global IQ scores. Similar to valproic acid, carbamazepine has been associated with an increased risk of spina bifida, with an incidence of about 1% (Rosa, 1991).

Teratogenic effects of carbamazepine have also been found in mice and rats; however, they occurred mostly at high doses (Sullivan and McElhatton, 1977; Finnell et al., 1986; Vorhees et al., 1990). Reported malformations include cleft palate, dilated cerebral ventricles, and various visceral and skeletal abnormalities. Incidence and severity of malformations were less than those observed in rodents treated with other antiepileptic drugs.

There has been some debate on whether one of the metabolites of carbamazepine, carbamazepine-10,11-epoxide, may be responsible for the teratogenic effects (Lindhout et al., 1984). Both carbamazepine and phenytoin are oxidatively metabolized through the cytochrome P450 monooxygenase system to epoxide intermediates, which are substrates for microsomal epoxide hydrolase (Omiecinski, 2000). The increased incidence of teratogenic effects often observed following polytherapy with antiepileptic drugs (Koch et al., 1999; Holmes et al., 2001; Stoler, 2001) has often been ascribed to the ability of certain compounds (e.g., valproic acid) to inhibit the metabolism of these epoxides. Furthermore, as microsomal epoxide hydrolase presents two coding region polymorphisms leading to different enzymatic activities (Omiecinski, 2000), it has been suggested that such genetic differences may have a role in antiepileptic drug-induced teratogenesis (Lindhout, 1992). However, attempts to identify at-risk fetuses prenatally on the basis of low or deficient epoxide hydrolase have met only with limited success (Omiecinski, 2000). Similarly, no differences in susceptibility to carbamazepine or carbamazepin-10,11-epoxide-induced malformations were found in two strains of mice with high and low epoxide hydrolase activity levels (Finnell et al., 1986).

No studies were found on neurobehavioral effects in animals following perinatal exposure to carbamazepine; as mentioned, behavioral effects in children were mild and usually accompanied by other malformations. Likewise, there is very limited information on specific effects and/or mechanisms of carbamazepine on the nervous system. Chronic exposure of cerebral cortical cell cultures resulted in only minimal toxicity (Neale et al., 1985). However, a preliminary study by Ikonomidou et al. (2000) found that dosing rats postnatally with doses of carbamazepine slightly above the ED_{50} for anticonvulsant action resulted in widespread neurodegeneration in the brain, similar to that observed for phenytoin.

From the available data, it appears that carbamazepine is the least developmental toxicant among the major antiepileptic drugs, as evidenced by both animal and human studies, not withstanding its association with an increased risk of spina bifida. Further behavioral and mechanistic studies on its potential effects on the developing brain appear warranted however.

5. "New" Antiepileptics. Over the past 10 years a number of new antiepileptic drugs have entered the

TABLE 6
Long-term effects in adult men of in utero exposure to phenobarbital on IQ scores

	N	Observed Score	Predicted Score	P *Value*
Verbal IQ	33	100.7	107.9	0.04
<5,000[a]	13	103.3	107.6	0.19
>5,000	20	99.0	108.5	0.03
Performance IQ	33	99.8	104.8	0.13
Full scale IQ	33	100.4	106.9	0.06

[a] Total phenobarbital dosage (mg).
Adapted from Reinisch et al. (1995).

worldwide market (McCabe, 2000; Sabers and Gram, 2000; Perucca, 2001; Wallace, 2001). Among these, four drugs act primarily on the GABAergic system: vigabatrin, which elevates GABA levels by inhibiting GABA transaminase; tiagabine, which achieves the same result by inhibiting GABA uptake; gabapentin, a cyclic analog of GABA which also enhances GABA synthesis; and topiramate, which acts on a novel site on the $GABA_A$ receptor (Czuczwar and Patsalos, 2001). Additional compounds act mainly by inhibition of use-dependent, voltage-sensitive sodium channels (e.g., lamotrigine and oxcarbazepine, a keto-analog of carbamazepine) (Perucca, 2001; Wallace, 2001).

Limited information exists on the potential toxicity and neurotoxicity of these drugs to the developing fetus. It has been suggested that these compounds may be "safer" than traditional anticonvulsants, as pregnancy outcomes have generally been favorable, and no consistent pattern of malformations has emerged (Morrell, 1996). Animal studies, however, indicate that all these compounds are embryotoxic, and skeletal abnormalities (delayed ossification) have been reported (Morrell, 1996; Perucca, 2001). Topiramate has been shown to cause limb agenesis at high doses (Morrell, 1996). This compound was excreted in the milk of lactating rats, with a milk/maternal plasma ratio of 0.8:1.1, suggesting that it would be excreted in human milk to a higher degree than other anticonvulsants (Bar-Oz et al., 2000). Use of lamotrigine during pregnancy indicates an incidence of congenital malformations of 6.5% compared with 3 to 5% in controls (Reiff-Eldridge et al., 2000). Clearly, studies are needed to assess the teratogenic potential of these newer compounds when used in monotherapy (Lowe, 2001). Furthermore, the possibility that more subtle neurobehavioral effects may be present in the offspring as a result of exposure during pregnancy needs to be investigated in humans as well as in animal models. Given the interactions of these new antiepileptics with the GABAergic system and the sodium channels, some degree of developmental neurotoxicity might be expected based on recently reported findings (Ikonomidou et al., 2000, 2001).

IV. Anxiolytics and Mood Stabilizers

The onset of bipolar disorders in women often occurs during childbearing years, which complicates treatment decisions because of the possibility of conception while taking medications. Recurrence of mania or bipolar depression is not uncommon during pregnancy, although it remains to be clarified whether gestation is associated with either enhanced or reduced risk of relapse of mania or bipolar depression (Viguera and Cohen, 1998). Management of pregnant women with these psychiatric illnesses poses several concerns, primarily regarding teratogenic potential of mood-stabilizing drugs (Iqbal et al., 2001). Indeed, women treated with mood stabilizers who become pregnant are commonly considered at high risk for offspring complications during pregnancy and during lactation. The risk of these medications includes direct neonatal toxicity and the potential for longer-term neurobehavioral sequelae, in addition to teratogenic effects. Therefore, the prescription of such drugs during pregnancy and lactation requires critical attention to the timing of exposure, dosage, duration of treatment, and fetal susceptibility. The neurobehavioral impact of untreated mania or depression on the developing brain also has to be taken into account. This section reviews the developmental toxicity of benzodiazepines and lithium, as that of other mood stabilizers such as valproic acid and carbamazepine is discussed in the previous section.

A. Benzodiazepines

Benzodiazepines (BZDs) are highly lipid-soluble substances that readily reach the fetus following maternal administration (Mandelli et al., 1975). Diazepam (the prototype of this class of drugs) and its active metabolites have been detected in neonatal rat brain following prenatal exposure over gestational days 13 to 20 (Simmons et al., 1983). The BZDs are anxiolytic, sedative, myorelaxant, and anticonvulsant compounds that exert their pharmacological effects in the adult by modulating the action of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor (Braestrup and Squires, 1978). BZDs achieve their effects by allosterically increasing the chloride conductance when GABA binds to its receptor, and the site mediating the pharmacological actions is referred to as the central-type BZD receptor. BZDs also interact in the brain with the peripheral-type BZD receptor, considered to be located mainly on mitochondrial membrane (Anholt et al., 1986). The precise role of the peripheral-type receptor in brain function is still under investigation; however, action at this site as well as interaction with neurosteroids, may account for some of the effects of prenatal exposure to BZDs (Kellogg et al., 1998). Prenatal exposure to BZDs in the rat has been linked to subsequent altered binding to this site (Schlumpf et al., 1993) and altered mitochondrial function (Miranda et al., 1989). In adults, action at the mitochondrial BZD receptor stimulates steroid synthesis in the brain (Korneyev et al., 1993), and specific neurosteroids are potent agonists at the $GABA_A$ receptor (Rupprecht and Holsboer, 1999). Furthermore, drug action at the mitochondrial BZD receptor can affect $GABA_A$ receptor function (Costa et al., 1994). Therefore, regardless of the primary site of interaction of BZDs within the fetal brain (i.e., central or mitochondrial site), altered $GABA_A$ receptor function could be one consequence.

Studies performed in the 1970s through the early 1980s found an association between gestational exposure to BZDs and fetal toxicity, such as reduced fetal body weight (Guerriero and Fox, 1977; Buttar, 1980), enhanced mortality, increased miscarriage rates (Stenchever and Parks, 1975), and diminished postnatal

survival (Guerriero and Fox, 1977). However, later studies were unable to confirm these observations (Cagiano et al., 1990). Structural abnormalities were also found in rodents following in utero BZD exposure, with an enhanced frequency in cleft palate (Miller and Becker, 1975; Barlow et al., 1980), exencephaly, and limb malformations, as well as rib defects at higher doses (Buttar, 1980). Differences in sample size, exposure length, type of BZD administered, and the animal species used might explain the lack of consistency in the findings regarding the potential teratogenic effects of in utero BZD exposure reported in the literature.

A large number of studies have shown that pre- and/or postnatal exposures to BZDs have short- and long-lasting effects on brain chemistry and behavior. Overall, these effects appear to be highly dependent upon the time of exposure and often emerge after the onset of puberty, and some of the reported functional disturbances also appear to be gender-specific. The mechanisms whereby early BZD exposure can provoke so many different effects remain still elusive, but consideration of the main sites of interaction in the brain can provide testable hypotheses. Investigations on possible changes in BZD receptor sites induced by prenatal BZD administration gave conflicting results, since increases, decreases, or no alterations in both BZD receptor affinity and density were observed (Massotti et al., 1980; Livezey et al., 1986; Kellogg et al., 1991). Furthermore, changes were often found to be transient or to occur only in some brain areas (Rothe and Bigl, 1989). Comparison among different studies is confounded by the use of different BZD compounds, a variety of exposure protocols, and different experimental procedures. Contrasting results were also obtained with regard to the GABA-gated chloride channel. For example, no change in GABA-dependent chloride uptake was found in animals exposed prenatally to BZD, whereas gender-specific enhanced inhibition of uptake by the GABA antagonist bicuculline was observed (Bitran et al., 1991). In rats gestationally treated with BZDs, GABA-dependent chloride uptake was significantly decreased at 1.5, 6, and 12 months of age (Koff and Miller, 1995). Decrements in pentylenetetrazole-induced seizure threshold and GABA-dependent chloride uptake suggest reduction in both BZD and GABA transmission efficacy after gestational exposure to lorazepam. Together with the reduced binding of the chloride channel ligand [^{35}S]*t*-butylbicyclophosphorothionate at 6 weeks of age (Miller et al., 1991), these data appear consistent with changes in coupling of $GABA_A$ receptor subunits.

The persistence of behavioral and biochemical alterations after prenatal BZD exposure suggests a permanent changes in $GABA_A$ receptor structure or function. Late gestational treatment of rats with diazepam produced subtle changes in the development of emotionality in rat pups (Cagiano et al., 1990). In particular, the duration of ultrasonic calls during the first weeks of postnatal life was markedly affected by prenatal administration of diazepam. Since it was suggested that the BZD/GABA receptor-chloride channel complex plays a role in the physiological mediation of rat pup ultrasonic isolation calls (Insel et al., 1986), the alterations in the ultrasonic vocalization suggests an impaired ontogenesis of these systems. Mice prenatally treated with oxazepam were found to be markedly hypoactive at the end of the second postnatal week; moreover, they showed a reduced hyperactive response to an amphetamine challenge (Alleva et al., 1985), whereas in adulthood they exhibited selective impairment of active avoidance but no changes in scopolamine-induced hyperactivity and passive avoidance (Bignami et al., 1992). Perinatal treatment with diazepam did not alter basal dopamine turnover in the prefrontal cortex or striatum or in any of the mesolimbic sites examined, except for the nucleus accumbens and ventral tegmental area, in which turnover was decreased. However, the magnitude of stress-elicited increase in prefrontal cortical dopamine turnover was significantly decreased and resulted in a stress-induced enhancement of turnover in striatum. These findings suggest that, although perinatal exposure to BZDs may alter basal dopaminergic function in some regions, certain enduring changes in other mesotelencephalic dopamine sites are revealed only under peculiar conditions, such as environmental stress, suggesting that developmental BZD exposure may result in a reduced ability to cope with stress in the adult (Deutch et al., 1989; Gruen et al., 1990).

Prenatal BZD administration was also reported to reduce [^{3}H]dihydroalprenolol binding to β-adrenoceptor sites in discrete brain areas, whereas postnatal exposure caused only a transient decline in the frontal cortex (Rothe and Langer, 1988), indicating again the importance of the time of exposure. Prenatal exposure to diazepam led to a reduced concentration and release of norepinephrine in the hypothalamus, but such effects were not apparent until after the onset of puberty (Kellogg and Retell, 1986). Also, this same exposure influenced some parameters of sexual activity in adult (120-day-old) male rats (Cagiano et al., 1990). Several investigations have shown that prenatal BZD exposure induces gender-dependent behavioral changes often related to the time of exposure. For example, administration of diazepam during the third week of pregnancy modified performance in the acquisition and retention of a simultaneous choice discrimination task in male rats, whereas postnatal exposure affected female animals primarily (Frieder et al., 1984). Prenatal BZD exposure can also result in a reversal of typical gender-related responses. Novel versus familiar environments remarkably affect social interaction occurring between two adult male rats, with the novel environment clearly decreasing social interaction when compared with results in a familiar surrounding (File, 1988). Conversely, the nature of the environment does not influence social

interaction between two adult female rats. Interestingly, prenatal treatment with BZDs made social interaction in adult male rats unreactive to the nature of the environment (Kellogg et al., 1991). In contrast, female animals appeared to be reactive to the nature of the environment, suggesting that exposure to BZDs during sensitive periods of brain development may reverse gender-specific environmental influences on social behaviors (Kellogg, 1999).

In comparison with effects induced by prenatal exposure to BZDs, there are much fewer data on the consequences of BZDs administration during early postnatal life. Learning and retention deficits, as well as increased activity in an open field, were reported in adult male rats neonatally exposed to BZDs (Frankova and Jakoubek, 1974; Fonseca et al., 1976; Frieder et al., 1984). These animals also exhibited increased aggressivity and reduced anxiety, depending on the drug and experimental situation (File, 1986a,b). Other studies did not confirm some of these findings (Wang and Huang, 1990). However, on the basis of the available data, it is possible to speculate that neonatal BZD exposure may induce mild and prolonged behavioral changes.

Mechanistic studies have investigated whether perinatal exposure to BZDs may affect the composition of $GABA_A$ receptor subunits. As the developmental expression of subunits and $GABA_A$ receptor sensitivity are strongly associated (Verdoorn et al., 1990), developmental BZD exposure may alter the relative balance of $GABA_A$ receptor isoforms during the perinatal period and during adulthood. Chronic treatment of cultured neurons with GABA or $GABA_A$ antagonists induces changes in the expression of $GABA_A$ receptor subunit mRNAs (Baumgartner et al., 1994; Platt et al., 1996; Lyons et al., 2000). Prolonged exposures to ligands that bind to distinct modulatory sites on $GABA_A$ receptors were also found to cause changes in $GABA_A$ receptor mRNA levels in neuronal cultures (Zheng et al., 1996; Liu et al., 1997) and in adult animals (Chen et al., 1999b; Tietz et al., 1999). Since alterations of cortical $GABA_A$ receptor sensitivity to both positive and negative modulators were found in adult male rats exposed in utero to BZDs (Bitran et al., 1991; Kellogg et al., 1991), it is possible that prenatal diazepam exposure may modify the levels of expression of discrete $GABA_A$ receptor isoforms.

The action of BZDs at $GABA_A$ receptors in utero could also influence neural differentiation and growth by altering, for example, the expression of trophic factors. In hippocampal neurons, stimulation of GABA receptors activated voltage-gated calcium channels and induced *c-fos* immunoreactivity, an index of neural activation (Berninger et al., 1995). Furthermore, this treatment increased levels of BDNF (brain-derived neurotrophic factor) mRNA. BDNF is a member of the neurotrophin family of neurotrophic factors (Barde, 1990) involved in the synaptic remodeling of the nervous system. These factors are crucial to the survival of neurons and play a role in the differentiation process (Snider and Johnson, 1989). Therefore, alteration of BDNF expression during early development could have a marked impact on the developmental process. BDNF-deficient mice display normal levels of GABA and of GABAergic neurons in the cerebral cortex and hippocampus but have significantly reduced expression of neuropeptides and calcium binding proteins in the cortex, hippocampus, and striatum. Prenatal exposure to diazepam was found to induce gender-related effects on BDNF mRNA levels during late fetal and early postnatal development (Kellogg et al., 2000). The gender-specific nature of such effect could derive from a possible interaction of cellular responses to drug action with the trophic actions of specific sex steroids (Fig. 1). Putative estrogen response elements have been recognized on BDNF genes (Sohrabji et al., 1995), and aromatization of testosterone to estrogen is considered a crucial factor in sexual differentiation (Hutchison et al., 1997; McEwen, 1983). Therefore, the effects of GABA modulation on BDNF expression could influence the transcription action of estrogens in male brains. Furthermore, in specific brain areas, calcium-binding proteins are sexually dimorphic. In fact, the levels of calbindin-D28k in the medial basal hypothalamus of males were increased compared with female rats during late fetal development (Lephart, 1996). Such sexually dimorphic distribution could modulate the effect of

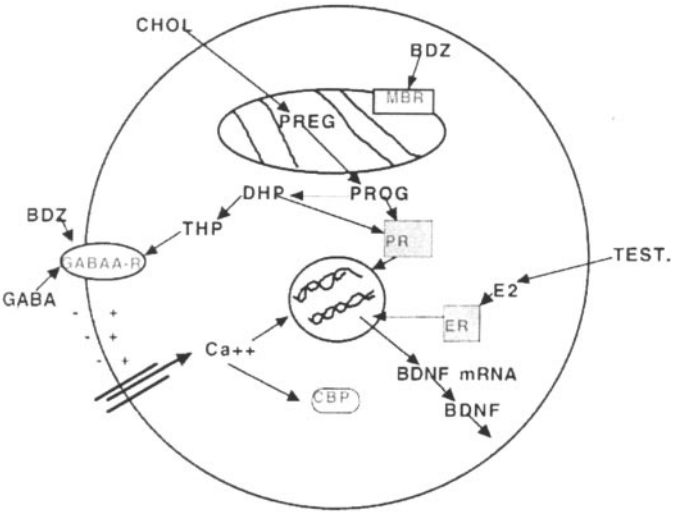

FIG. 1. Proposed mechanisms of action of BZDs in developing neurons. BZD can interact with the $GABA_A$ receptor. GABA stimulation in culture has been associated with increased calcium flux and increased BDNF mRNA levels. Calcium influx can influence gene transcription via several routes. Sexual dimorphism from this route of interaction could arise from sexually dimorphic distribution of specific calcium binding proteins (CBP) or the sex-specific presence of testosterone (TEST.) which can be aromatized to estradiol (E2). This, in turn, by binding to the estrogen receptor (ER), can influence BDNF transcription. BZDs also bind to the mitochondrial BZD receptor (MBR), whose stimulation affects de novo steroid synthesis in brain. An effect on steroid synthesis could influence cellular levels of 5α-reduced steroids such as DHP (5α-pregnan-3–20-dione) and THP (allopregnanolone). DHP can bind to progesterone receptors (PR) and influence gene transcription, whereas THP is a positive modulator of $GABA_A$ receptors. Other abbreviations: PREG, pregnenolone; PROG, progesterone; CHOL, cholesterol. Adapted from Kellogg (1999) with permission.

GABA-mediated calcium influx with severe consequences on several cellular processes. As mentioned earlier, BZDs can also interact with the mitochondrial BZD receptor, a site that has been associated with regulation of steroidogenesis in several organs (Papadopoulos et al., 1990; Gavish et al., 1992). Drugs acting at the mitochondrial BZD receptor modulate de novo neurosteroidogenesis (Korneyev et al., 1993), apparently by facilitating the intramitochondrial flux of cholesterol (Krueger and Papadopoulos, 1990). Therefore, it is possible to speculate that BZDs, during fetal development, could influence brain steroidogenesis rather than gonadal steroidogenesis. This in turn could affect levels of 5α-reduced steroids, which are potent modulators of $GABA_A$ receptor function (Fig. 1). On the basis of this evidence, it is clear that there are multiple mechanisms whereby BZDs present in the brain during development could affect $GABA_A$ receptor functioning and thus influence neural growth and differentiation.

In early case-control studies, a significant association was found between gestational BZD exposure, mainly during the first trimester, and some structural anomalies, such as cleft lip and cleft palate (Saxen and Lahti, 1974; Saxen and Saxen, 1975). Diazepam is the BZD most often involved, with a 4-fold enhancement in cleft lip (with or without cleft palate) among neonates, whose mothers had taken diazepam during the first 3 months of gestation (Safra and Oakley, 1975). This may be due to the fact that diazepam accounts for approximately 70% of BZDs prescribed during pregnancy (McGrath et al., 1999). However, the lipophilic nature of diazepam (van der Kleijn, 1969), its high storage in animal fat tissue (Marcucci et al., 1968), its easy penetration into the brain, and its long retention in neural tissues in monkeys (Idanpaan-Heikkila et al., 1971) suggest that human tissues may act as depot for this BZD. Abnormalities of the abdomen, feet and toes, skeletal deformities, and abnormalities of the lung, heart, gastrointestinal tract, and kidney are other malformations found following BZD administration during pregnancy (McGrath et al., 1999). Furthermore, an embryofetopathy associated with the regular use of BZDs has been described, that resembles fetal alcohol syndrome (Laegreid et al., 1987). Indeed, Laegreid and colleagues (1992a) reported a specific "BZD syndrome," observed among seven infants with dysmorphism in a prospective study of 36 mothers who took BZDs during pregnancy. Five mothers had taken diazepam and two had taken oxazepam (an active metabolite of diazepam). The clinical findings of this BZD syndrome included Möbius syndrome, Dandy-Walker malformation with lissencephaly, polycystic kidney, submucous cleft hard palate, microcephaly, dysmorphism, varying degrees of mental retardation, convulsions, and neonatal abstinence syndrome (Gerhardsson and Alfredsson, 1987). Low birth weight and small head circumference were also reported in a study of 17 infants born of women who had taken diazepam or other BZDs during pregnancy (Laegreid et al., 1992b). The weight of children returned to normal values by 10 months, but head circumference was still smaller than expected at 18 months (Laegreid et al., 1992a).

In contrast to these findings, a number of other studies failed to find a significant association between gestational exposure to BZDs and the occurrence of fetal malformations (Hartz et al., 1975; Delaney, 1983). Rosenberg et al. (1983) reported that exposure to diazepam during the first trimester of pregnancy was not associated with an increase of neonatal oral cleft. Similarly, an additional risk due to gestational exposure to BZDs was not observed among infants already at higher risk because of other factors such as a family history of oral cleft.

A meta-analysis of cohort and case control studies indicated that only the latter showed a small but significant increased risk for malformations of the oral cleft (Dolovich et al., 1998). However, case control studies for oral cleft were heterogenous, which decreases the reliability of the results (Dolovich et al., 1998). More case control studies would be required to clarify the impact of the association between prenatal BZD exposure and the occurrence of oral cleft; presently, although occasional reports have associated the therapeutic use of diazepam with congenital malformations, the bulk of evidence indicates that its use during gestation does not significantly induce marked adverse effects on child development. Thus, BZDs should be considered to pose a low risk for structural teratological effects when used at the lowest possible dosage and for the shortest time during pregnancy. On the other hand, BZDs should be avoided, or the dosage decreased, in the weeks before delivery, as they may induce neonatal withdrawal syndrome, floppy infant syndrome, or various effects in the newborn including muscular hypotonicity, failure to feed, impaired temperature regulation, apnea, and low Apgar scores (Whitelaw et al., 1981; Fisher et al., 1985).

With regard to potential functional sequelae following prenatal BZD exposure, limited information is available in humans. In a study by Hartz and colleagues (1975), no evidence was found that BZDs may be associated with detrimental effects on the maturing brain, as judged by mental scores at the age of 8 months and IQ scores at 4 years. It was also reported that in approximately 550 children exposed in utero to BZDs, no significant adverse effects on neurobehavioral development and IQ could be found. However, most children exhibited a slower development during the first year, with a full recovery by 4 years of age (McElhatton, 1994). In another study, in utero exposure to BZDs may induce a general delay in mental development up to 18 months of age (Viggedal et al., 1993). In summary, given the limited information available, no clear association between the administration of BZDs during pregnancy and alterations in neurobehavioral development in humans can be established. However, the paucity of data and the

lack of long-term follow-up studies and of appropriate behavioral testing, together with the results of animal studies, suggest that caution should be exerted.

A final note on novel benzodiazepine-receptor agonists such as zopiclone, zolpidem, and zaleplon: systematic studies evaluating the safety in pregnant women as well as their effects on human reproduction and development are lacking. However, experiments performed in rats have shown that prenatal exposure to zolpidem induces adverse maternal and fetal effects, including dose-related maternal lethargy, ataxia, and a dose-related trend to incomplete ossification of fetal skull bones (Friedman and Prenez, 1988).

B. Lithium

In addition to altering cation distribution in the brain, therapeutic levels of lithium exert significant effects on the metabolism of the monoamines involved in the pathophysiology of affective disorders, as well as on the molecular mechanisms implicated in signal transduction or in other cellular events, including gene regulation (Jope, 1999). Both the adenylate cyclase and phosphoinositide second messenger systems are deeply influenced by lithium, albeit in different manners, including actions on G proteins and protein kinase C (Jope, 1999; Manji et al., 1999). Evidence that lithium inhibits inositol monophosphatase, decreases brain inositol concentrations, and reduces inositol 1,4,5-triphosphate accumulation in rodent cerebral cortex has led to the inositol depletion hypothesis of its mechanism of action. However, further investigation using cerebral cortex of a number of laboratory animals, including primates has found that lithium actually enhances inositol 1,4,5-triphosphate concentrations, if supplemental inositol is provided (Manji et al., 2000). Long-term lithium administration has been reported to decrease concentrations of myristolated alanine-rich C kinase substrate, a protein involved in neurotransmission (Watson and Lennox, 1996). Moreover, therapeutically equivalent concentrations of lithium in cultured neurons have enhanced transcriptional factor binding to both activated protein 1 and cAMP-responsive element (Jope, 1999). Finally, lithium has also been shown to inhibit glycogen synthase kinase-3, a protein kinase implicated in neuronal cytoskeletal development (Chen et al., 1999a). If any of the above reported biochemical effects would explain its respective mechanism of action in bipolar illness, it remains unclear.

Investigations aimed at testing the potential detrimental effects of lithium in developing animals have used a variety of experimental procedures, so that the incongruity of experimental protocols has weakened confidence in the overall conclusions. However, in spite of such limitations, the data provided by these studies have shown that developmental toxicity may occur in rats (Marathe and Thomas, 1986; Hoberman et al., 1990) and in mice (Szabo, 1969, 1970) exposed to lithium during gestation. Observations of developmental toxicity, which includes, among others, increased prenatal mortality, decreased weight, nephrotoxicity, and skeletal abnormalities, are in agreement with pharmacokinetic data, which show that lithium is readily absorbed and distributed in fluids and tissues (Stokinger, 1981). The dose-response curve for lithium toxicity in rodents appears relatively steep (Trautner et al., 1958; Mroczka et al., 1983), and damaging effects occur throughout the dose range. An in vitro study has shown that explanted embryos from rats or mice are vulnerable to primary lithium toxicity in the absence of any confounding maternal factors (Hansen et al., 1990). Developmental toxicity may occur also postnatally, with detrimental effects essentially represented by growth retardation and higher mortality in the exposed litters, both in mice (Smithberg and Dixit, 1982; Mroczka et al., 1983) and in rats (Gralla and McIlhenny, 1972; Christensen et al., 1982). Such effects were associated with lithium doses lower than those inducing prenatal toxicity.

Both pre- and postnatal lithium exposures adversely affect the ability of offspring in two tests of learning and memory (Hsu and Rider, 1978). In offspring of rats exposed to lithium during gestation and through lactation, significant delays in developmental indices such as eye opening and startle response were observed (Sechzer et al., 1986). Some effects were still present well after the end of treatment, such as changes in spontaneous motor activity, which was significantly decreased at 4 months of age. In another study, different degrees of impairment of learning and memory in a shock avoidance test were reported following developmental exposure to lithium (Sechzer et al., 1987). More recently, evidence has been provided showing that chronic treatment of pregnant rats with lithium at doses similar to those used in the prophylaxis of bipolar disorders aggravates the delay in behavioral development of pups induced by stress associated with limited water intake and handling (Teixeira et al., 1995). Although these findings support the notion that lithium exposure induces functional teratogenic effects in the developing brain at low doses, the small number of animals used and the sparse reporting of information (e.g., lack of blood lithium levels or the inability to precisely ascertain litter incidences) weaken their relevance and usefulness. Thus, only scant information remains regarding the impact of lithium pre- and postnatal exposure on offspring behavior.

Several studies have also investigated gross morphological effects caused by lithium, with little attention given, however, to the molecular pathogenetic mechanisms underlying such structural changes. Limited biochemical evidence has been provided showing cerebrum and cerebellum cell loss (as reflected in DNA content) at concentrations higher than therapeutic levels in humans (Dixit and Smithberg, 1988). In a study in which the effect of lithium on the development and survival of cultured cerebellar granule neurons was examined, it

was reported that treatment of immature cells results in neuronal death via the induction of apoptosis. In sharp contrast to its effect on developing neurons, lithium inhibits apoptosis in fully differentiated neurons (D'Mello et al., 1994). Thus, the same agent exhibits dramatically contrasting actions on cerebellar granule neurons, depending on the stage of development. This possibility may have important implications, since it is possible to speculate that during neuronal development, when maximal cell death occurs as part of a physiological process, lithium might perturb developmental processes, accelerating neuronal apoptosis in the immature brain.

In summary, there are sufficient, albeit limited, data to suggest that lithium exposure in developing animals, at doses equal to those achieved during human therapy, causes developmental toxicity. This is relevant to humans, since developmental adverse effects frequently occur in humans and animals at similar lithium serum levels.

Although rodent studies suggest that teratogenic effects may occur in offspring exposed in utero and during lactation to high doses of lithium, such results cannot be directly extrapolated from one animal species to humans. Lithium appears to travel freely across the human placenta, and a comparative evaluation of lithium concentrations in maternal and umbilical cord blood at delivery has shown that infant serum levels were the same as the mother's, but decrease quickly (Schou and Amdisen, 1975; Sykes et al., 1976). In the 1970s, lithium treatment during pregnancy was strongly associated with congenital malformations, in particular with Ebstein's anomaly (a severe tricuspid valve insufficiency) in the offspring (Schou, 1998). A re-evaluation of the therapeutic risk of in utero exposure to this agent concluded that it is lower than originally assumed (Cohen et al., 1994). Indeed, initial reports from the Registry of Lithium Babies, founded in the late 1960s, suggested that children exposed in utero to lithium during the first trimester showed a frequency 5 and 400 times the expected rate, respectively, for congenital malformations and Ebstein's anomaly. However, since the registry was characterized by an intrinsic bias toward overreporting of abnormal outcomes, the documented occurrence of an increased rate of cardiovascular malformations occurring following lithium exposure has been critically reviewed. Two cohort investigations, exploring the outcome of pregnancies following lithium administration during the first trimester, were unable to demonstrate a marked correlation between gestational exposure to the drug and congenital malformations, as initially documented (Kallén and Tandberg, 1983; Jacobson et al., 1992). Similarly, four case control studies, exploring the frequencies of in utero lithium exposure in children with Ebstein's anomaly and in a control group, have failed to prove a relationship with first-trimester drug exposure as strong as previously presumed (Kallén, 1988; Sipek, 1989; Edmonds and Oakley, 1990; Zalzstein et al., 1990). Thus, epidemiological studies without the selection bias of the registry have given more reassuring results, even if a pooled review of the above reported investigations has substantiated the notion that first-trimester exposure to lithium is associated with an enhanced risk of congenital malformations (Cohen et al., 1994) when compared with the baseline rate reported in the general population. Specifically, the estimated risk of Ebstein's anomaly after maternal treatment during the first trimester of gestation has been evaluated to range from 10 to 20 times that documented in the general population.

The potential adverse effects of lithium exposure in utero are not limited to cardiovascular malformations. Several groups have reported nontoxic goiters in the infants of mothers treated with lithium during pregnancy; mothers of these children also had nontoxic goiters (Schou et al., 1968; Karlsson et al., 1975). However, a definitive relationship between lithium exposure during pregnancy and thyroid goiter has not been established (Nars and Girard, 1977; Cohen et al., 1994). Other detrimental effects that have been reported occasionally are polyhydramnios after fetal polyuria, stillbirth, and neonatal jaundice (Moore, 1995). Floppy baby syndrome, characterized by cyanosis and hypertonicity, has also been described (Woody et al., 1971; Schou and Amdisen, 1975). On the other hand, information on behavioral outcomes of children exposed to lithium during pregnancy is still limited. A study was conducted in Scandinavian children exposed in utero to lithium and born without malformations (Schou, 1976). Their development was compared with that of their nonexposed siblings who shared a number of genetic and environmental conditions. This 5-year follow-up study revealed no significant differences between the two groups. Previous studies recommended switching prepregnancy prophylaxis with lithium to an alternative mood stabilizer, such as carbamazepine or valproic acid (Markovitz and Calabrese, 1990). These recommendations expressed concerns about the risk of malformations associated with the exposure to lithium during the first trimester of pregnancy. However, on the basis of recent data, the rate of neural tube defects following gestational exposure to carbamazepine and valproic acid suggests that lithium may be considered the "lesser of the three evils" (Viguera and Cohen, 1998). Indeed, craniofacial abnormalities and possible cognitive dysfunctions, occurring even after exposure to these agents late in pregnancy, in addition to neural tube defects, may represent adverse effects more devastating to long-term development than those associated with lithium exposure (Schou, 2001).

In conclusion, the management of bipolar disorders in women who plan to conceive or who are pregnant gives rise to significant challenges. Available results suggest that pregnancy is not protective and the risk for relapse after discontinuation of treatment is similar in pregnant and in nonpregnant patients with 50% of relapsing within 6 months (Viguera et al., 2000). A number of

investigations have confirmed that the risk of congenital malformations is low when lithium is administered during pregnancy, mainly considering that there is no prophylactic alternative with a lower risk-benefit ratio (Schou, 2001). The medication should be continued after the delivery to avoid postpartum exacerbation of illness (Marcus et al., 2001).

V. Antidepressants

The relationship between reproductive events in women and depression has received increasing attention. Up to 70% of pregnant women may exhibit depressive symptoms, with 10 to 16% of them fulfilling diagnostic criteria for major depressive disorder (Affonso et al., 1990; Weissman and Olfson, 1995). The decision regarding initiation or continuation of antidepressant pharmacotherapy during gestation is often complicated, as the desire to minimize fetal antidepressant exposure has to be weighed against the risk of the potential adverse impact of the maternal illness. Depression itself may lead to inadequate nutrition, disrupted sleep, poor prenatal care, poor pregnancy outcomes, and substance abuse (Istvan, 1986; Steer et al., 1992; Perkin et al., 1993; Cummings and Davies, 1994; Orr and Miller, 1995). More dramatic outcomes such as fetal abuse or maternal suicide may be the disastrous consequences of unmedicated depression during pregnancy (Burt and Hendrick, 1997). In addition, untreated depression during gestation can adversely affect mother-infant attachment, and infant development and maternal stress during pregnancy may induce neurobiological changes in the offspring (Lundy et al., 1999; Taylor et al., 2000). Extensive results from animal research suggest that maternal stress during pregnancy has adverse consequences for offspring growth (Schneider et al., 1999), learning ability (Weller et al., 1988), and postnatal development (Fride and Weinstock, 1984). These results suggest that there may be benefits to mother and infant from initiating or continuing antidepressant treatment during gestation, yet an understanding of the potential risks connected with in utero antidepressant exposure is required to make informed and patient-tailored choices.

Antidepressants are classified according to their structure or the central neurotransmitter system they act upon (Table 7). The older tricyclics (TCAs), related cyclic antidepressants, and the monoamine oxidase inhibitors (MAOIs), have been more recently joined by the selective serotonin reuptake inhibitors (SSRIs), the reversible inhibitors of monoamine oxidase type A (e.g., moclobemide), and lately by the serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine), or the selective norepinephrine reuptake inhibitors (e.g., reboxetine) (Kent, 2000). Other antidepressants that do not fall into these classes include viloxazine, trazodone, nefazodone, mianserin, and mirtazapine, among many others.

TABLE 7
Major antidepressant drugs

Tricyclic antidepressants	Imipramine
	Amitriptyline
	Desipramine
	Clomipramine
	Nortriptyline
Atypical antidepressant	Mianserin
	Maprotiline
	Nefazodone
	Trazodone
	Nomifensine
Monoamine oxidase inhibitors	Phenelzine
	Isocarboxazide
	Brofaromine
	Moclobemide
	Chlorgyline
	Tranylcypromine
Selective serotonin reuptake inhibitors	Fluoxetine
	Citalopram
	Fluvoxamine
	Paroxetine
	Sertraline
Novel antidepressants	Reboxetine
	Mirtazapine
	Milnacipran

The first agents used successfully were the TCAs, which have a wide range of neuropharmacological effects, in addition to their presumed primary action consisting of the inhibition of the transport of NE and, variably, of 5-HT into nerve endings, thus leading to sustained facilitation of noradrenergic and serotoninergic transmission. Among the conventional TCAs, there is relatively little selectivity between NE and 5-HT uptake, and it is not clear which type of activity is more important for the antidepressant effect. Interpretation is made difficult by the fact that the major metabolites of TCAs have considerable pharmacological activity (in same cases greater than the parent drug) and often differ from the parent drug with respect to their NE/5-HT selectivity. In addition to their effects on amine uptake, most TCAs affect one or more types of neurotransmitter receptors, including those for acetylcholine (muscarinic), histamine, and 5-HT. These effects of TCAs most likely do not contribute to their antidepressant effects but are responsible for various side effects (Thase and Nolen, 2000).

The view that antidepressant drugs work simply by enhancing monoamine neurotransmission at some key sites in the brain is no longer tenable, having been effectively weakened by the temporal discrepancy between the pharmacodynamic and therapeutic actions of TCAs. Unfortunately, despite much experimental work directed at the problem, there is still no convincing mechanistic theory with which to define the mechanism of action of TCAs. In the absence of a simple mechanistic theory to account for their antidepressant action, it is useful to look for pharmacological effects that various drugs have in common, particularly on slow changes

that may show a similar time course with the therapeutic effect. This approach has led to the discovery that certain monoamine receptors, particularly β- and α_2-adrenoceptors, are consistently down-regulated following chronic antidepressant treatment. α_1-Adrenoceptors are not consistently affected, whereas 5-HT_2 receptors also appear down-regulated. Impaired presynaptic inhibition, secondary to down-regulation of autoreceptors, might facilitate monoamine release and thus facilitate transmission (Frazer, 1997). Additionally, it has been reported that repeated exposure to TCAs results in a significant increase of cAMP level and changed activity of protein kinases, including those affecting cytoskeletal and other structural proteins that may influence neuronal growth and sprouting (Racagni et al., 1991; Wong et al., 1991). Finally, protracted administration of TCAs has been observed to modify the expression of a variety of nuclear genetic regulatory factors, such as cAMP-responsive element and brain-derived neurotrophic factor (Duman et al., 1997; Siuciak et al., 1997).

SSRIs preferentially inhibit the reuptake of 5-HT, compared with NE, and have limited direct action on other neurotransmitter sites (Baldessarini, 2001). Specific SSRIs differ in selectivity and potency for the reuptake of 5-HT, and the two parameters are not interdependent. Thus, citalopram is the most selective of the currently available 5-HT reuptake inhibitors, whereas paroxetine is the most potent (Masand and Gupta, 1999). Enhanced 5-HT availability induced by SSRIs can activate a variety of receptors; in particular, terminal 5-HT autoreceptors are down-regulated following protracted treatment with these agents, reflecting their ability to facilitate serotoninergic neurotransmission by increasing neurotransmitter synthesis and release (Chaput et al., 1991). This has been suggested to play a role in their antidepressant effects and to be a critical step in the signal transduction in cellular events that result in altered patterns of gene expression, mRNA translation, or protein modification (Azmitia and Whitaker-Azmitia, 1995). Similarly, the enhanced availability of NE induced by NE reuptake inhibitors (e.g., reboxetine) decreases transmitter synthesis and release, possibly through a prolonged activation of presynaptic α_2-adrenoceptors (Potter et al., 1998). Subsequent stimulation of postsynaptic α_1-receptors on other monoaminergic neurons may facilitate serotonin and, perhaps, dopamine transmission (Leonard and Richelson, 2000). The phenylpiperazine compound nefazodone and, to a lesser extent, the structurally related trazodone, display a weak blocking effect on 5-HT_{2A} receptor, which is believed to be involved in antidepressant effects. Both agents exert antagonistic effects at presynaptic autoreceptor to enhance 5-HT transmission (Baldessarini, 2001).

Mirtazapine and mianserin exhibit similar chemical structure and share a variety of pharmacodynamic effects. Both drugs display antagonistic actions at several postsynaptic 5-HT receptors, including the 5-HT_{2A} and 5-HT_{2C} subtypes. In addition, both induce down-regulation of α_2-adrenergic and 5-HT_{2A} receptors. The reduced effectiveness of α_2-adrenoceptors, located either as autoreceptors on noradrenergic neurons or as heteroreceptors on serotoninergic terminals, enhances synthesis and release of both NE and 5-HT. Similarly, the decreased efficacy of the inhibitory 5-HT_{2A} heteroreceptors acting at the presynaptic level of noradrenergic fibers results in a net increase in NE release. All these effects are probably implicated in the antidepressant action of both compounds (Golden et al., 1998).

The monoamine oxidases (MAOs) are flavoproteins found on the outer membranes of mitochondria that catalyze the oxidative deamination of a variety of amines. Free cytoplasmic and extraneuronal neurotransmitter amines would be susceptible to MAO metabolism. However, under normal conditions the classic neurotransmitters metabolized by MAO (NE, dopamine, and 5-HT) are preferentially stored in vesicles where they are not exposed to MAO. Of the two major molecular species of MAO, type A is selectively inhibited by clorgyline and prefers 5-HT as substrate; type B is inhibited by selegiline and prefers phenylethylamine as substrate. MAOIs in clinical use are site-directed and irreversible, such as phenelzine, isocarboxazide, pargyline, clorgyline, or selective short-acting and reversible, such as moclobemide and brofaromine. The ability of MAOIs to act as antidepressants is assumed to reflect increased availability of monoamine transmitters in the brain or the sympathetic nervous system, but this assumption is difficult to prove. Indeed, the human brain expresses both enzymes, but MAO_B predominates (80-95%) over MAO_A, whereas in the rat brain MAO_A is predominant over MAO_B (Krishnan, 1998). Convincing evidence has shown that in human brain serotoninergic neurons contain predominantly MAO_B, whereas catecholaminergic neurons contain MAO_A. Both MAO_A and MAO_B are present in glial cells, suggesting that the two forms of the enzyme are independently regulated and perform different functions. The main effect of MAO inhibition is to induce a marked increase in the concentration of a number of indirectly acting "trace amines," including phenylethylamine, *meta*- and *para*-tyrosine, and octopamine. These trace amines are able to strongly affect uptake, release, or both of catecholamines and 5-HT at nerve terminals. They may also behave as neuromodulators through direct effects on receptors for catecholamines or 5-HT (Baldessarini, 2001). The mechanisms underlying the antidepressant effects of MAOIs are not well understood and may not be fully explained by their ability to protect monoamines from destruction. Indeed, some evidence for a common mechanism of action with TCAs comes from studies demonstrating that both drugs produce a similar delayed down-regulation of β-adrenoceptors and 5-HT_2 receptors (Krishnan, 1998).

A. Tricyclic and Atypical Antidepressants

Investigations in laboratory animals have shown that prenatal exposure to TCAs does not lead to marked teratogenic effects. Indeed, amitriptyline caused a low incidence of skull defects in rabbits (Khan and Azam, 1969) and, at equivalent doses, did not induce significant malformations in rodents; two analogous agents, butriptyline and protriptyline, did not display teratogenic effects (Schardein, 2000). Imipramine was teratogenic in hamsters (Geber at al., 1980) and rabbits (Harper et al., 1965) but had no effects in three other species, including mouse (Harper et al., 1965), rat (Aeppli, 1969), and two species of primates, bonnet and macaques rhesus (Hendrickx, 1975). The imipramine metabolite, desipramine, and clomipramine, showed no teratogenic effects in rodents and rabbits (see Dollery, 1999, for references). Altogether, these studies do not reveal a marked association between fetal exposure to TCAs and congenital malformations in laboratory animals. Similarly, investigations in rodents and rabbits also failed to show any evidence of a potent teratogenicity caused by atypical antidepressants, including mianserin, maprotiline, and nefazodone (see Dollery, 1999, for references). In humans, an early report suggested an association between the maternal use of these drugs during the first trimester and the birth of infants with severe limb reduction defects (McBride, 1972). However, later studies failed to support such finding. Three prospective studies and at least 10 retrospective studies that examined the risk for organ dysgenesis after first-trimester exposure to TCAs documented that the use of these compounds in early pregnancy does not carry any increased risk of malformations (Cohen and Rosenbaum, 1998, and references herein). Other antidepressants, such as atypical agents including mianserin, maprotiline, nefazodone, and trazodone, also did not induce any detrimental reproductive effect, but no studies have been performed to definitively document their safety in humans (Robert, 1996).

Animal studies have shown that prenatal treatment with both typical and atypical antidepressants can lead to profound neurochemical and neurobehavioral changes in the offspring of exposed dams (Cuomo, 1987). For example, rats prenatally exposed to TCAs such as imipramine and clomipramine exhibited decreased hypothalamic dopamine levels at 30 days of age. The number of cortical β-adrenoceptors was significantly decreased in 14- and 30-day-old animals, even though a partial recovery was observed at the latter age (Jason et al., 1981). Although a reduction in β-adrenoceptor number is also elicited by chronic imipramine administration in adult animals, it is of interest to note that binding affinity is decreased in adult animals, whereas it is increased at 30 days following prenatal exposure, suggesting the presence of different compensatory mechanisms for the earlier functional receptor alterations as the animal matures (Jason et al., 1981). Some of the changes in neurotransmitter function produced by prenatal exposure to imipramine persisted up to several months after birth. Also, gestational exposure to the atypical antidepressants mianserin and nomifensine consistently reduced cortical β-adrenoceptor density in rats at PD 25, whereas the same drugs did not induce such effect in adult rats (De Ceballos et al., 1985), suggesting again a different response of the developing brain. It should be emphasized, however, that these results indicate similar but more pronounced effects in developing animals than in adults. This is different from the findings obtained, for example, with prenatal administration of the antipsychotic haloperidol, which caused a decrease in dopamine D_2 receptors in the offspring, whereas the opposite effect was observed in nursing dams or adult rats (Rosengarten and Friedhoff, 1979).

A number of studies have examined the potential long-lasting effects of tricyclic and atypical antidepressants on the 5-HT system after gestational exposure. No variations in 5-HT content or 5-HT turnover were detected in different brain areas of 9-month-old rats, whose mothers were administered imipramine during gestation and nursing (Tonge, 1974). On the other hand, in rats prenatally exposed to amitriptyline, 5-HT was significantly decreased in the brain of 1-day-old rats, whereas levels of 5-hydroxyindole acetic acid, the major 5-HT metabolite, were increased at postnatal week 1 (Bigl et al., 1982).

Maternal treatment with clomipramine, iprindole, or mianserin reduced cortical binding sites labeled with [^{3}H]spiperone or [^{3}H]ketanserin in the progeny at PD 25 by about 25%, without modifying the ligand affinity. On the other hand, prenatal exposure to the atypical antidepressant nomifensine augmented by approximately 60% the density of these binding sites and, at the same time, decreased their affinity (De Ceballos et al., 1985). It is interesting to note that the reduction in serotonin 5-HT_2-binding sites after repeated treatments of adult rats with amitriptyline and mianserin returned to control values in 10 days (Peroutka and Snyder, 1980; Blackshear and Sanders-Bush, 1982), whereas changes caused by fetal exposure to tricyclic and atypical antidepressants were more persistent. This provides yet more support to the notion that the developing brain responds differently to these compounds. This concept is also strengthened by the findings that prenatal exposure to clomipramine and fluoxetine, two selective 5-HT blockers, as well as to two MAOIs, clorgyline and selegyline, down-regulated [^{3}H]imipramine-binding sites in rats at PD 25. Conversely, desipramine and nomifensine, selective inhibitors of NE and dopamine reuptake, respectively, were ineffective in this respect (Table 8). Changes in [^{3}H]imipramine binding sites were not generally observed after long-term treatment with the same drugs in adult rats (Montero et al., 1990). This discrepancy provides additional and convincing evidence of the higher vulnerability of the fetal brain to the actions of antide-

TABLE 8
Neurochemical effects of prenatal exposure to typical and atypical antidepressants in rats

Antidepressants	[^{3}H]Imipramine Binding Sites in Cerebral Cortex
Clomipramine	↓
Fluoxetine	↓
Clorgyline	↓
Desipramine	NE
Nomifensine	NE

NE, no effect; ↓, decreased effect.
Adapted from Montero et al. (1990).

pressants. Finally, prenatal exposure to conventional TCAs such as amitriptyline may also affect the development of interrelated neurotransmitter systems. The concentration of both NE and GABA was increased on PD 15 and 21, respectively. Similarly, activities of both glutamate decarboxylase and acetylcholinesterase were increased in the brains of 12- and 21-day-old rats, respectively (Bigl et al., 1982).

Parallel studies have shown that such biochemical alterations are accompanied by a variety of long-lasting neurobehavioral changes. Prolonged administration of amitriptyline to pregnant rats significantly altered locomotor activity in young offspring (Bigl et al., 1982), whereas prenatal exposure to other TCAs, such as imipramine and desipramine, produced short- and long-term neurobehavioral changes such as delay in the development of the surface righting reflex and of negative geotaxis (Jason et al., 1981), impaired locomotion and learning (Coyle and Singer, 1975), and altered levels of locomotor activity (Cuomo et al., 1984). Prolonged prenatal administration of clomipramine increased baseline acoustic startle in female rats, and both genders showed greater between-day response decrements. Interestingly, in the social interaction test of anxiety, both males and females exposed prenatally to this antidepressant revealed a similar profile to that seen after chronic administration of benzodiazepines in adults (File and Tucker, 1984). Moreover, changes in neonatal reflexes (righting responses, forelimb placing, and grasping), were also found in rats maternally exposed to clomipramine. Atypical antidepressants, such as mianserin and viloxazine, also caused behavioral changes (e.g., increased locomotor activity in 23-day-old rats) in the offspring (Cuomo et al., 1984).

With the exception of nomifensine, tricyclic and atypical antidepressants are not believed to exert pronounced effects on the brain dopaminergic system. However, spontaneous locomotion (a typical dopamine-related behavior) was reduced in 25-day-old rats exposed in utero to clomipramine, mianserin, and iprindole. Conversely, in rats of the same age, spontaneous locomotor activity was significantly enhanced if animals were exposed in utero to nomifensine (Del Rio et al., 1988). Similar results were also found following prenatal treatment with *d*-amphetamine (Bigl et al., 1982). Furthermore, in utero exposure to antidepressants, such as clomipramine, iprindole, and nomifensine, but not mianserin, was found to potentiate the hyperactivity induced by moderate doses of the dopaminergic agonist apomorphine, suggesting hypersensitivity of dopamine receptors (Del Rio et al., 1988). In this context, a more pronounced hyperactive response to amphetamine was also documented in 21-day-old rats gestationally exposed to imipramine (Ali et al., 1986).

The above findings infer that prenatal exposure to antidepressants significantly affects the developing brain. This assumption is further reinforced by observations of long-lasting neurochemical and behavioral alterations occurring in rodents after antidepressant administration during the early postnatal period. Neonatal treatment with desipramine was shown to lengthen free-running period, increase circadian amplitude, and enhance voluntary alcohol intake of male rats (Rosenwasser and Hayes, 1994), whereas clomipramine caused increased immobility in the forced swim test, enhanced voluntary alcohol intake, change in REM sleep patterns and decreased aggressiveness, reward-seeking, and sexual activity (Mirmiran et al., 1981; Hilakivi et al., 1984; Vogel et al., 1990, 1996; Velazquez-Moctezuma and Diaz Ruiz, 1992). Additionally, in rats given clomipramine postnatally, electrophysiological studies of serotoninergic activity in the dorsal raphe nucleus revealed decreased spontaneous firing rate (Yavari et al., 1993) and hyposensitivity to the inhibitory effects of acute citalopram, a 5-HT reuptake blocker (Maudhuit et al., 1995). Decreased hypothalamic 5-HT levels following neonatal clomipramine treatment provided further evidence for a down-regulation of 5-HT systems (Feenstra et al., 1996). Moreover, nomifensine administration to rodents in the early postnatal period induced changes in open field behavior and increased voluntary alcohol intake in adults because of long-lasting alterations in brain monoamines (Hilakivi et al., 1987).

A comparison of the behavioral and neurochemical effects produced by prolonged developmental or adult exposure to desipramine and mianserin, which preferentially influence the noradrenergic system, indicates that chronic treatment of adult rats caused a significant attenuation of clonidine-induced depression of locomotor activity (Table 9). Parallel neurochemical findings show reduced cortical normetanephrine concentrations as well as a significant attenuation of the effects of a challenge dose of clonidine on normetanephrine content (Table 9) (Racagni et al., 1982, 1983). Conversely, early postnatal administration of these antidepressants (from day 2 after birth until day 21) produced differential effects: desipramine increased normetanephrine levels in the cerebral cortex of 23-day-old pups, whereas mianserin had no effect. Moreover, a single dose of clonidine decreased normetanephrine levels in controls or in chronically desipramine-pretreated rats, whereas it was ineffective when chronic mianserin was given. At PD 23,

TABLE 9
Behavioral and neurochemical changes produced by developmental or adult exposure to typical and atypical antidepressants in rats

Endpoint	Desipramine Exposure during		Mianserin Exposure during	
	Development	Adulthood	Development	Adulthood
Ambulation (long-term effects)	↓	NE	↓	NE
Clonidine-induced decrease in ambulation	↓	↓	NE	↓
Cortical normetanephrine concentrations	↑	↓	NE	↓
Clonidine-induced decrease in normetanephrine concentrations	NE	↓	↓ ↓	↓

NE, no effect; ↓, decreased effect; ↓ ↓, effect is abolished.
From Cuomo (1987) and references therein.

the decrement of locomotion induced by clonidine was attenuated in postnatally desipramine-exposed rats, but not in the mianserin group (Table 9). Furthermore, unlike prolonged treatment during adulthood, the locomotor activity of desipramine- and mianserin-pretreated animals was significantly reduced 70 days after antidepressant withdrawal (Racagni et al., 1982, 1983). Since neurochemical and behavioral consequences of chronic administration of antidepressants are indicative of adaptive changes in some neurotransmitter systems in the mature rat, the effects occurring in developing rats following a prolonged postnatal exposure to these agents suggest that the adaptive mechanisms are not yet operative in the immature brain. Further insight into the mechanisms implicated in the changes associated with developmental antidepressant exposure was provided by investigations monitoring *c-fos* gene expression as a molecular index of neural activity. The increased expression and the regional variations in the distribution pattern of *c-fos* transcript observed in the brain of young adult rats after neonatal injection of nomifensine suggested that ontogenic changes in messages and information processing could be associated with developmental alterations induced by drug exposure during sensitive periods of maturation (Murata et al., 2001).

All of these findings confirm that tricyclic and atypical antidepressants exert a profound impact on the maturing brain. To provide further evidence indicative of antidepressant effects on the developmental nervous system, amitriptyline was found to affect neurite outgrowth from embryonic cerebral explant cultures at concentrations close to those used therapeutically (Wong et al., 1991). It is likely that other antidepressants, primarily tricyclics, may exhibit similar actions.

B. Monoamine Oxidase Inhibitors

Gestational exposure to MAOIs has been related to fetal growth retardation in animals (Poulson and Robson, 1964). However, no fetal adverse effects were found in the offspring of rats treated with tranylcypromine (Gracious and Wisner, 1997) or moclobemide (Rybakowski, 2001). Scant information is available regarding the teratogenic potential of MAOIs in humans. Indeed, a recent review of the literature found few reports on the use of these compounds during pregnancy. The Collaborative Perinatal Project in the 1970s followed 21 mother-child pairs: an enhanced relative risk of 3.4 was determined, based on three cases of congenital malformations (Heinonen et al., 1977). However, the small sample size, the lack of description of the type of abnormalities, and the inclusion of isoniazid in the exposed group limits interpretation of these results. On the other hand, further case reports failed to demonstrate any positive significant association between the prenatal exposure to phenelzine, tranylcypromine, and moclobemide and infant malformations (Gracious and Wisner, 1997; Rybakowski, 2001).

Monoamine neurotransmitters exert important actions on the development of the immature mammalian brain before assuming their role as neurotransmitters. As the endogenous levels of these transmitters are highly regulated by MAO, any change in this enzyme should have a profound effect on brain development. Indeed, changes in open field behaviors, including locomotion, rearing, grooming, and active avoidance responses were found in rats exposed in utero to MAOIs such as iproniazid or isocarboxazid (Drago et al., 1985). Perinatal administration of clorgyline and deprenyl, which inhibit MAO_A and MAO_B, respectively, induced an increase in open field activity and a deficit in passive avoidance in rat offspring (Whitaker-Azmitia et al., 1994). These behavioral effects were associated with changes in the development of the cortical 5-HT system, with a significant reduction of serotonergic innervation at PD 30. These animals also exhibited stereotyped behaviors, seizures, and visual deficits. Interestingly, the altered behaviors observed in rats had a striking resemblance to those present in patients with atypical Norrie's disease, an X-linked recessive disorder associated with a deletion of genes encoding for MAO_A and MAO_B (Sims et al., 1989).

Clorgyline administration to mouse pups during the first postnatal week resulted in behavioral abnormalities such as agitation, trembling, hunched posture, and increased righting time; however, these behavioral alterations were no longer observable 24 h after the last injection (Vitalis et al., 1998). Clorgyline-treated pups exhibited increased 5-HT immunostaining throughout

the brain and impaired barrel field formation in the primary somatosensory cortex (Cases et al., 1996). This cytoarchitectural alteration was comparable with that observed in Tg8 mice, animals deficient in the gene encoding for MAO_A, in which abnormal barrel size and enhanced tangential extent of thalamocortical arbors were observed (Cases et al., 1995). The causal role of excessive 5-HT concentrations during the critical period of barrel formation was supported by evidence that previous administration to mice of an inhibitor of 5-HT production, parachlorophenylalanine, but not of methylparatyrosine, an inhibitor of catecholamine synthesis, restored cortical patterns (Cases et al., 1996). Thus, MAO_A inhibition, resulting in increased brain levels of 5-HT, affected barrel development during the entire first postnatal week with a sensitive period between postnatal days 0 and 4 (Vitalis et al., 1998). Finally, it is noteworthy that, similar to what was observed in normal mice following MAO_A inhibitors, MAO_A-deficient mice exhibited enhanced aggression, in addition to a selective increase of emotional, but not motor, learning (Kim et al., 1997).

C. Selective Serotonin Reuptake Inhibitors

Fluoxetine was found to disrupt the normal cranial morphogenesis in mouse embryo, possibly by the blockade of the 5-HT transport into differentiating craniofacial epithelia (Shuey et al., 1992). Despite these findings, most available data from animal studies support the conclusion that the widely used SSRIs, such as fluoxetine, fluvoxamine, paroxetine, citalopram, and sertraline, have no significant detrimental effect on the progeny at maternally nontoxic doses (Byrd and Markham, 1994; see Dollery, 1999, for references; Vorhees et al., 1994).

Human studies also confirm animal experiments by showing that the new SSRIs do not appear to increase the risk of congenital malformations when used in the recommended doses. The most studied SSRI with respect to its use in pregnancy has been fluoxetine. No study found increased rates of major fetal malformations or miscarriages among women treated with fluoxetine, when compared with women exposed to tricyclic antidepressants (Pastuszak et al., 1993) or nonteratogens (Chambers et al., 1996; Goldstein et al., 1997). In one study comparing first-trimester and third-trimester exposure, an association was found between first-trimester exposure to fluoxetine and increased incidence of three or more minor anomalies, although the nature of these alterations was not specified (Chambers et al., 1996). These results were not confirmed by a later investigation (Cohen et al., 2000). Studies focusing on the teratogenic potential of sertraline, paroxetine, and fluvoxamine in humans failed to demonstrate the occurrence of an increased risk of congenital malformations. A recent report revealed almost identical rates of malformations (9 of 222 versus 9 of 235) between the SSRI and control groups, suggesting that a greater number of cases in each group would not modify previous results (Kulin et al., 1998). Similarly, although early observations linked the use of citalopram during the first trimester of pregnancy to optic nerve hypoplasia and septum pellucidum defects, detected long after the perinatal period, a further investigation based on a prospective recording of drug use in early pregnancy did not confirm evidence of teratogenic effects associated with gestational citalopram exposure (Ericson et al., 1999).

Ontogenesis of the rat 5-HT transporter and 5-HT receptors indicates a rapid increase during the perinatal and early postnatal period to reach adult levels by the end of the third postnatal week, with a time course that closely parallels synaptogenesis (Igvy-May et al., 1994). Recently, many investigations have been devoted to the exploration of the neurobehavioral and neurochemical effects of developmental exposure to SSRIs, and most research has focused on fluoxetine because of its high selectivity and negligible affinity for several receptor subtypes. Prenatal exposure to fluoxetine significantly diminished 5-HT content in the frontal cortex of prepubescent but not adult rats, whereas in adult offspring a significant decline was found only in midbrain (Cabrera-Vera et al., 1997). Prenatal fluoxetine also decreased the density and the function of hypothalamic $5\text{-}HT_{2A/2C}$ receptors; overall, the data suggest that neurochemical changes are both age-dependent and site-specific (Cabrera and Battaglia, 1994). Prenatal exposure to fluoxetine also reduced 5-HT-stimulated phosphoinositide hydrolysis in 25-day-old pups, whereas chronic treatment of adult animals with the same drug or prenatal exposure to either desipramine or tianeptine did not modify inositol phosphate accumulation (Romero et al., 1994).

Fluoxetine, at doses not toxic to dams, did not cause behavioral abnormalities as assessed by locomotor activity, spontaneous alternation, passive avoidance, and water-maze performance in the offspring (Vorhees et al., 1994). Despite variations among mammalian species, it is of interest to note that maternal fluoxetine administration resulted in decreases in low-voltage electrocortical activity and in REM sleep in the sheep fetus (Morrison et al., 2001). Whether these alterations persist longer than the infusion period or whether fluoxetine administration is associated with postnatal behavioral consequences remains to be determined. In this regard, the fluoxetine-elicited reduction in REM sleep could be particularly significant, given its likely importance for normal brain development during fetal and postnatal periods (Mirmiran and van Someren, 1993; Richardson, 1994). Mice offspring prenatally exposed to paroxetine performed motivation and learning and memory tasks in manners that were indistinguishable from the placebo-controlled group (Christensen et al., 2000). In a previous study examining multiple noncognitive behavioral tasks, no statistical differences were found between mice

offspring exposed in utero to paroxetine or placebo in many early developmental tasks, including negative geotaxis, homing, social play, and exploratory activities (Coleman et al., 1999). Performance during a depression task (forced swim) and anxiety tasks (elevated plus maze) was indistinguishable between the two treatment groups, regardless of gender. However, offspring exposed to paroxetine had a minor increase in separation vocalization and a significant increase in male aggression during cage changing (Coleman et al., 1999).

In studies exploring potential effects of early postnatal exposure to SSRIs, it was reported that prolonged selective inhibition of 5-HT uptake by fluoxetine in preweaning rats decreased overall locomotor activity, altered responses to repeated acoustic startle stimuli, and blunted quipazine effects in response to novelty in a gender-related manner. Additionally, this exposure decreased density of dopamine D_1 binding sites in mesolimbic regions and diminished the expression of mRNA for the 5-HT transporter in the dorsal raphe (Dow-Edwards, 1998). These findings indicate that postnatal administration of fluoxetine results in persistent changes in the responsiveness of both indolaminergic and dopaminergic systems in rat brain. Recently, it has also been reported that rat pups separated from mothers on postnatal day 14 and socially isolated for 1 week display a decrease in cell proliferation and enhanced rate of apoptosis in the dentate gyrus of the hippocampus which was prevented by fluoxetine (Lee et al., 2001). Thus, fluoxetine may be considered as an agent able to counteract the effects of maternal separation. This is relevant, since enduring effects of early maternal separation may have implications for adult-period vulnerability to the emergence of psychiatric disorders (Andersen et al., 1999). Finally, citalopram administered to neonatal rats reduced aggression in adult animals, suggesting that neuroadaptive mechanisms developed during the neonatal period may last into adult life (Manhaes de Castro et al., 2001).

Apart from the perinatal syndrome induced by late gestational exposure to TCAs, exposure in utero to either TCAs or SSRIs did not adversely affect the neurobehavioral development of children tested up to preschool age (Misri and Sivertz, 1991; Nulman et al., 1997; Kulin et al., 1998). Children exposed to either the SSRI fluoxetine or a TCA in utero were studied to assess cognition, language, and behavior at 16 to 86 months of age and were compared with a nonexposed control group. Mean global IQ scores were not different among the three groups, suggesting that in utero antidepressant exposure had no effect on cognition. Likewise, verbal comprehension and expressive language skills were similar among the groups, indicating that language development was not negatively affected. Finally, there were no significant differences in temperament, mood, arousability, activity level, distractibility, or behavior of the children in the three groups, suggesting that in utero exposure to either tricyclic antidepressants or fluoxetine does not adversely influence the neurodevelopment of preschool children (Nulman et al., 1997). Follow-up data of neonatally exposed to antidepressants are scarce. With the exception of doxepin, no acute detrimental effects were described, whereas the risk of long-term neurobehavioral consequences remains unclarified (Wisner et al., 1996; Yoshida et al., 1997; Llewellyn and Stowe, 1998; Misri et al., 2000; Hendrick et al., 2001).

D. Novel Antidepressants

To our knowledge, there are insufficient studies to assess the safety of the novel antidepressants during pregnancy in humans. Preliminary results appear to indicate that the use of venlafaxine in pregnant patients does not increase the rates of congenital malformations above the baseline rate of 1 to 3% (Einarson et al., 2001). Few investigations have also focused on the behavioral consequences of perinatal treatment with the novel antidepressants, such as venlafaxine, mirtazapine, reboxetine, nefazodone, and milnacipran. A recent report found no detrimental effects in rats gestationally exposed to venlafaxine (da Silva et al., 1999). There are no published reports showing neurochemical and behavioral effects induced by perinatal administration of novel antidepressants. In the absence of animal or human data, their use during pregnancy would best be cautioned until further research clarifies their potential long-term behavioral teratogenicity in exposed infants.

As a general comment on the use of antidepressants during pregnancy, it is interesting to note an apparent discrepancy between animal and human studies. Indeed, whereas animal laboratory investigations demonstrate abnormalities in brain receptors and neurotransmitter functioning in offspring exposed in utero to a variety of antidepressants, human data appear so far reassuring, since no persistent functional toxicity has been reported after maternal administration of such medications. However, results from preclinical research suggest that appropriate caution and vigilance should be exerted, keeping in mind that no proof of risk is not equivalent to proof of safety. In conclusion, although the substantial clinical experience with the use of antidepressants in pregnancy is encouraging, further clinical studies, especially long-term neurobehavioral follow-ups, are warranted, since most investigations and surveys had relatively small sample sizes and could not completely estimate the risk for rare events.

VI. Neuroactive Herbal Drugs

Herbal medicines and dietary supplements have become a popular option in health care and a growing business, with an estimated market of $4 billion in the United States and $6.7 billion in Europe (Gruenwald, 2000). Of notice is that the use of herbal remedies is increasing at a substantial pace; for example, U.S. sales

for St. John's wort were reported to be $48 million in 1997 and $140 million in 1998; sales of ginkgo biloba increased from $90 million in 1997 to $150 million in the following year (Table 10) (Landes, 1998; Blumenthal, 1999). Such substantially increasing popularity of herbal medicines is thought to arise from a general dissatisfaction of the general public for conventional pharmacotherapy, the perception that these medications are considered "natural," thus devoid of adverse effects, the effectiveness of media and marketing campaigns, and their easy availability in health and food stores (Astin, 1998; Beaubrun and Gray, 2000; Ernst, 2002a). With the exception of Germany, sale of herbal medicines is not strictly regulated (Schulz et al., 1998). In the United States, herbal preparations are regulated as dietary supplements under the Dietary Supplement Health and Education Act of 1994, which does not require demonstration of effectiveness nor extensive proof of safety, although there are limits and requirements with regard to health claims (Hathcock, 2001). Although issues of effectiveness are being addressed by an increasing number of clinical studies (albeit with many methodological problems and contrasting results), the issue of safety is not being investigated to a great extent. Yet there is increasing evidence that herbal medicines may have adverse health effects due to one or more of the pharmacologically active or inactive ingredients, the presence of contaminants such as metals or pesticides, and interactions with lifestyle factors (e.g., alcohol) or, more prominently, with other conventional medications (Klepser and Klepser, 1999; Izzo and Ernst, 2001; Ernst, 2002a). Most of the issues on efficacy and safety stem from the lack of regulation as well as from a lack of standardization; products may indeed vary greatly in their composition depending on variation in the raw plant material (due to genetic factors, climate, soil, growing conditions, etc.), methods of preparation, and solvent used in the extraction process (Schulz et al., 1998).

Four of the most commonly used herbal medications are taken for the prevention or treatment of psychiatric symptoms, which is the most rapidly growing segment of the herbal product market (Wong et al., 1998; Fugh-Berman and Cott, 1999; Beaubrun and Gray, 2000; Assemi, 2001; Ernst, 2002a). These are St. John's wort, used for the treatment of depression; ginkgo biloba, used to prevent or treat memory problems including dementia; kava, taken as an anxiolytic; and valerian, used as a sleep remedy. In general, very little information exists on the potential adverse health effects of these medicinal herbs on the developing fetus or the newborn when taken during pregnancy or lactation. Because of this paucity of data, use of these herbs during pregnancy or lactation is contraindicated (Wong et al., 1998). However, a recent survey reported that 73% of nurse-midwives in North Carolina recommend herbal therapies to pregnant women (Allaire et al., 2000), and in another survey in Rhode Island, 9.1% of women reported use of herbal drugs during pregnancy (Gibson et al., 2001). Other surveys in Europe, Australia, and Africa provided similar results (Ernst, 2002b). Indeed, cautionary warnings are not believed to reach the general public and, on the basis of the known pharmacological actions of these medicinal herbs, neurofunctional effects on the developing brain may be expected. In the following sections, the major characteristics, pharmacological actions, and known or potential neurodevelopmental effects of St. John's wort, ginkgo, kava, and valerian are discussed.

TABLE 10
U.S. sales of major herbal medicine products

Herbal Remedy	1997	1998	Percentage Increase
	Millions of U.S. $		
Ginkgo biloba	90	151	68
St. John's wort	48	140	192
Ginseng	86	96	12
Garlic	72	84	17
Echinacea	49	70	43
Saw palmetto	18	32	78
Kava	3	17	466

From: Landes (1998) and Blumenthal (1999).

A. St. John's Wort

St. John's wort (*Hypericum perforatum* L.) is a common roadside plant which has been used for medicinal purposes for over 2000 years (Schulz et al., 1998) and is currently one of the most commonly used herbal remedies in Europe and the United States (Beaubrun and Gray, 2000; Di Carlo et al., 2001). Flower extracts are used as an antidepressant, and indeed a large number of studies have shown that St. John's wort is effective in the treatment of mild to moderate depression (Linde et al., 1996; Linde and Mulrow, 2000; Barnes et al., 2001). In most studies, St. John's wort was significantly superior to placebo and similarly effective as standard antidepressants; furthermore, the proportions of patients reporting side effects were lower for hypericum. A recent study, however, reported a complete lack of effects of a standardized hypericum preparation (LI 1660) in major depressive disorders (Hypericum Depression Trial Study Group, 2002).

Extracts of St. John's wort contain a large number of anthraquinone derivatives (e.g., hypericin), flavonoids, prenylated phloroglucinols (e.g., hyperforin), tannins, phenols, and other constituents (Barnes et al., 2001). It has been assumed that hypericin is the main active ingredient, and indeed preparations are standardized on the basis of hypericin content. However, recent evidence suggests that hyperforin may be one of the major constituents required for antidepressant activity (Laakman et al., 1998). A number of in vitro and in vivo studies have evidenced interactions of St. John's wort extracts with neurotransmitter systems, which may underlie its antidepressant action. Thus, inhibition of MAO_A and

MAO_B were reported, although concentrations of hypericum required are unlikely to be attained in humans after oral administration (Cott, 1997; Barnes et al., 2001). On the other hand, inhibition of serotonin uptake, as well as the uptake of other monoamines, is achieved at lower concentrations and is also caused by hyperforin (Barnes et al., 2001; Di Carlo et al., 2001). Alterations of β-adrenoceptors and $5\text{-}HT_2$ receptors have also been reported following in vivo treatments (Müller et al., 1997). Side effects of St. John's wort are generally mild, and animal studies indicate a low toxicity (Fugh-Berman and Cott, 1999). However, significant interactions with therapeutic drugs have been reported, with a reduction of their therapeutic effects, as in case of oral contraceptives, anti-human immunodeficiency virus compounds, cyclosporine, and anticoagulants, or an increased effect, when concomitant exposure to selective 5-HT reuptake inhibitors occurs (Barnes et al., 2001; Izzo and Ernst, 2001). Such interactions may be due to the ability of St. John's wort extracts to induce P-glycoprotein and some cytochrome P450 isozymes (Moore et al., 2000a; Assemi, 2001; Bray et al., 2002).

There is limited evidence that St. John's wort may have some mild effects on the developing fetus. In a series of studies, Rayburn et al. (2000, 2001a,b), investigated the effect of a standardized hypericum preparation (0.3% hypericin, 900 mg/day) given to mice for 2 weeks before mating and throughout gestation. No effects on body size, head circumference, or physical milestones were found in the offspring, with the exception of a lower body weight in male mice at birth. Other positive findings included a decreased percentage of male pups that successfully performed the negative geotaxis task (a test for vestibular and postural reflexes requiring motor coordination) and a transient hyperactivity of male pups on postnatal day 21. Female offspring exposed to hypericum required more time to learn the Morris maze task, but in several other behavioral tests no differences from controls were observed. In a similar study, rats were exposed to St. John's wort extract via the diet from gestational day 3 to postnatal day 21 (Cada et al., 2001). Dose exceeded those recommended in humans by 5- to 25-fold. A significant effect on body weight gain was observed in the offspring, but no changes were observed in open field activity, acoustic startling response, and various maze performances (Cada et al., 2001). These studies seem to indicate that St. John's wort may have only minor neurodevelopmental effects in mice or rats. Yet, as use of this medicinal herb occurs in pregnant and nursing women (Grush et al., 1998; Klier et al., 2002), caution should be used. In particular, the similitude of action with other antidepressants, in particular the effects on the serotoninergic systems, calls for further studies on the potential developmental neurotoxicity of St. John's wort.

B. Ginkgo Biloba

The ginkgo tree (*Ginkgo biloba* L.) is one of the oldest deciduous tree species on earth, and its fruit and leaf extracts have been used in popular medicine for centuries (McKenna et al., 2001). Ginkgo is used to prevent or treat memory problems or dementia. Evidence from randomized, controlled trials indicate that ginkgo extracts are effective in the treatment of psychopathological conditions and memory impairment caused by Alzheimer's and vascular dementia (Le Bars et al., 1997; Oken et al., 1998; Ernst and Pittler, 1999). In most studies, standardized extracts such as EGb761 or LI 1370 were used. Ginkgo extracts contain a large number of flavonoids, several diterpenes such as ginkgolides A, B, and C, and several other compounds, but there is no specific information on which one(s) would be responsible for the observed clinical effects. In vitro studies have shown that ginkgo extracts have neuroprotective effects against β-amyloid toxicity (Bastianetto et al., 2000) and act as antioxidants (McKenna et al., 2001). They also increase blood flow through small vessels and inhibit platelet aggregation (Kleijnen and Knipschild, 1992).

There are no studies on potential developmental effects of ginkgo biloba, but its use during pregnancy and lactation is contraindicated due to this lack of safety data (Wong et al., 1998). Two aspects, however, may raise some concerns or at least warrant further investigations. Ten phenolic compounds from ginkgo have been shown to inhibit phosphatidylinositol-specific phospholipase Cγ1 and the growth of several tumor cell lines (Lee et al., 1998). Such an effect may also hamper proliferation of neuronal and glial cells during embryogenesis. In another study, significant levels of colchicine were found in placental blood of patients using herbal dietary supplements (Table 11). The presence of colchicine in commercially available ginkgo biloba was also confirmed (Petty et al., 2001). As colchicine is a known antimitotic and has been shown to have teratogenic properties (Shepard, 1996), the rapidly growing fetus may be particularly vulnerable to its effects.

C. Kava

Kava (*Piper methysticum*) is a shrub cultivated throughout the South Pacific, and kava preparations are

TABLE 11
Colchicine in placental blood

Blood Sample Number	Colchicine
	μg/l
1	49
2	97
3	106
4	182
5	760
Herbal medicine	
Ginkgo biloba	26 (μg/tablet)
Echinacea	2 (μg/tablet)

Adapted from Petty et al. (2001).

made from the rhizome of the plant. Used by the natives of the Pacific islands as a recreational drink for its relaxant effects during social or cultural functions (Schulz et al., 1998), kava extracts are marketed as anxiolytics. A recent systematic review and meta-analysis of several clinical trials concluded that kava extracts are effective in reducing anxiety (Pittler and Ernst, 2000). When compared with treatments with benzodiazepines such as oxazepam or bromazepam, standardized kava preparations (WS 1490) proved to be similarly effective.

The active ingredients of kava appear to be kavapyrones and kavalactones such as methysticine and kavaine (Schulz et al., 1998). Kavapyrones have been shown to have various actions on neurotransmitter systems, including activation of GABA receptors, inhibition of NE uptake and of MAO_B activity, and decrease of glutamate release (Jussofie et al., 1994; Seitz et al., 1997; Uebelhack et al., 1998) but do not seem to directly interact with benzodiazepine receptors (Davies et al., 1992). Kavaine has been shown to block the voltage-dependent sodium channels (Glietz et al., 1995) and has pronounced L-type calcium channel-antagonistic properties, in addition to acting as a positive modulator of the early potassium outward current (Grunze et al., 2001). Major side effects of kava include scaly dermatitis (Norton and Ruze, 1994) and hepatotoxicity (Russmann et al., 2001); possible neurotoxicity is suggested by a recent case report on kava-induced parkinsonism (Meseguer et al., 2002).

There are no studies on the potential effects of kava extracts on the developing fetus, and because of this lack of safety data, kava is contraindicated during pregnancy and lactation (Wong et al., 1998; Beaubrun and Gray, 2000). However, the known pharmacological effects of the active principles of kava, particularly the interactions with $GABA_A$ receptors and sodium channels, suggest that the developing brain may be adversely affected by this herb.

D. Valerian

Valerian (*Valeriana officinalis* L.) has a long history of use in traditional medicine, particularly in Europe (Schulz et al., 1998). Preparations of valerian are used as a mild sedative and for induction of sleep (Houghton, 1999). However, a recent systematic review of randomized clinical trials of the use of valerian for insomnia concluded that the evidence for a positive effect of valerian is inconclusive (Stevinson and Ernst, 2000).

Valerian contains monoterpenes (e.g., borneol), sesquiterpenes (e.g., valerianic acid), and valepotriates (Houghton, 1999). Extracts of valerian have affinity for $GABA_A$ receptors, likely because of the relatively high content of GABA and glutamine in valerian itself (Cavadas et al., 1995). Endogenous GABA may also be responsible for the observed in vitro effects of valerian extracts on GABA uptake and release (Santos et al., 1994). As GABA does not readily cross the blood-brain barrier, the relevance of such in vitro findings to the in vivo action of valerian is questionable. However, valerianic acid has been shown to inhibit the catabolism of GABA and to increase GABA levels (Riedel et al., 1982). Interactions with $5\text{-}HT_{1A}$ and adenosine receptors have also been reported (Wong et al., 1998).

A single study on the developmental effects of valerian found no significant abnormalities in rats following gestational exposure to valepotriates (Tufik et al., 1994). As in the case of other herbal remedies, because of the lack of information on safety use of valerian is contraindicated during pregnancy and lactation (Wong et al., 1998). From the known biochemical effects of various valerian constituents and from its high GABA content, perturbation of the GABAergic system in the developing brain may be expected. Again, studies to explore this possibility are warranted.

VII. Future Prospects and Research Needs

This literature review has provided interesting and important observations that will require clarification in the future. First, it seems clear that in some instances, such as with antiepileptic agents, treatment during pregnancy can result in abnormal offspring, both in terms of structural teratogenesis and with regard to more subtle neurobehavioral effects. This conclusion is supported by animal data, as well as by human studies (Table 12). However, even in case of antiepileptic agents, knowledge of the mechanism(s) underlying teratogenic

TABLE 12
Summary of structural effects and neurofunctional sequelae of developmental exposures to psychotherapeutic drugs in animals and humans

	Animal		Human	
	Structural	Functional*	Structural	Functional
Antipsychotics				
Typical	+	+++	+	NI
Atypical	−	+	−	NI
Antiepileptics				
Valproic acid	+++	++	+++	+++
Phenytoin	+++	+++	+++	++
Phenobarbital	+	+++	+	++
Carbamazepine	+	NI	+++	+
New compounds	+	NI	+	NI
Anxiolytics/mood stabilizers				
Benzodiazepines	+	+++	+	+
Lithium	++	+	+(+)	NI
Antidepressants				
Tricyclics/atypical	−/+	+++	−/+	NI
MAO inhibitors	−/+	++	−, NI	NI
SSRIs	−	+	−	−, NI
Novel compounds	NI	NI	NI	NI
Herbal remedies				
St. John's wort	−	+	NI	NI
Ginkgo	NI	NI	NI	NI
Kava	NI	NI	NI	NI
Valerian	−, NI	NI	NI	NI

Symbols: −, no evidence of effects; −/+, contrasting evidence of effects; +, limited evidence of effects; ++, moderate evidence of effects; +++, strong evidence of effects; NI, none or little information available.
* Includes both neurochemical and behavioral effects.

and developmental neurotoxic effects is still very limited.

Second, for other classes of psychotherapeutic agents such as antipsychotics and antidepressants, there is an abundance of animal data indicating that perinatal exposure to these compounds causes long-lasting neurochemical and behavioral effects, yet human data are either not available or negative (Table 12). In very rare instances were long-term follow-up studies performed on the offspring exposed in utero to these agents. The lack of a clear-cut association in humans between exposure to certain psychotherapeutic agents and adverse outcomes in the progeny may instill complacency among physicians, whose primary obligation may be the health of the mother. However, there is no doubt from the review of the animal and the in vitro data that most of these drugs are indeed toxic to the developing nervous system. Why, then, are there are no clear indications in humans of potential adverse outcomes related to in utero exposure to psychotherapeutic drugs? An interesting analogy may be made with the case of lead, a widely distributed environmental pollutant. Lead exposure has been known since Roman times to be toxic to humans. However, the selective neurotoxicity of this ubiquitous compound to children only became clear since the 1980s when, by developing subtle neurobehavioral research techniques and by conducting careful follow-up studies, Needleman and his colleagues (1982) were able to show that blood levels of lead far below those considered safe for children, as indicated by the U.S. National Academy of Sciences (1972), were in fact causing dose-related alterations in IQ, reaction times, and behavioral problems in the classroom as evaluated by teachers. Later work showed more subtle effects even in the neonatal period (Needleman and Bellinger, 1994).

The importance of the lead studies is that most people did not consider this metal to be toxic at blood levels below 20 μg/dl and were therefore not interested in developing methodologies for measuring subtle effects. Given the apparent developmental toxicity of most psychotherapeutic agents in animals, it is likely that the paucity of reports of adverse effects in children is related to a lack of studies that use the battery of tests now available to measure subtle neurobehavioral changes in children. It is thus important to develop better research strategies, based perhaps on the lead toxicity model, to determine whether adverse effects are present in offspring of women treated during gestation for psychiatric and other nervous system disorders. As a large number of women are treated annually with psychotherapeutic drugs, one would desire not only anecdotal case reports from a clinician's office but large cohort studies that would provide sufficient statistical power. Neurobehavioral and other neurofunctional data should be correlated, if at all possible, with measurements of blood concentrations of the pharmacological agents and their metabolites, determined at birth (from umbilical samples) and during the neonatal period. These latter measurements may be particularly important if the infant is being nursed, as continuing exposure may ensue via the milk.

A third issue arising from this literature review has to do with the increasing use of herbal remedies by the general population, including pregnant women. As these preparations are seen as natural, they often instill a false sense of safety and the belief that they cause no adverse effects. Yet, if significant levels of pharmacologically active compounds are present in such phytotherapeutic agents, potential effects on the developing brain are to be expected. This area of research appears to be the weakest, both in terms of animal than human studies (Table 12).

Finally, one should note that in case of environmental agents (lead, as discussed, but also methylmercury, certain pesticides, polychlorinated biphenyls, etc.), attention and concern have shifted in the past decades from severe structural abnormalities to more subtle behavioral and neurochemical alterations present in the offspring following in utero exposure. It would seem that with psychotherapeutic drugs, even after any risk/benefit consideration, such concerns on possible neurofunctional sequelae of developmental exposure are certainly warranted from a scientific, clinical, and ethical point of view.

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