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REVIEW

Antidepressant therapy in epilepsy: can treating the comorbidities affect the underlying disorder?

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There is a high incidence of psychiatric comorbidity in people with epilepsy (PWE), particularly depression. The manifold adverse consequences of comorbid depression have been more clearly mapped in recent years. Accordingly, considerable efforts have been made to improve detection and diagnosis, with the result that many PWE are treated with antidepressant drugs, medications with the potential to influence both epilepsy and depression. Exposure to older generations of antidepressants (notably tricyclic antidepressants and bupropion) can increase seizure frequency. However, a growing body of evidence suggests that newer ('second generation') antidepressants, such as selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors, have markedly less effect on excitability and may lead to improvements in epilepsy severity. Although a great deal is known about how antidepressants affect excitability on short time scales in experimental models, little is known about the effects of chronic antidepressant exposure on the underlying processes subsumed under the term 'epileptogenesis': the progressive neurobiological processes by which the non-epileptic brain changes so that it generates spontaneous, recurrent seizures. This paper reviews the literature concerning the influences of antidepressants in PWE and in animal models. The second section describes neurobiological mechanisms implicated in both antidepressant actions and in epileptogenesis, highlighting potential substrates that may mediate any effects of antidepressants on the development and progression of epilepsy. Although much indirect evidence suggests the overall clinical effects of antidepressants on epilepsy itself are beneficial, there are reasons for caution and the need for further research, discussed in the concluding section.

Abbreviations

8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; ACTH, adrenocorticotrophin releasing hormone; AED, antiepileptic drug; DOI, 2,5-dimethoxy-4-iodoamphetamine; GAERS, Genetic Absence Epilepsy Rats from Strasbourg; GEPR, Genetically Epilepsy Prone Rats; HPA axis, hypothalamo-pituitary-adrenal axis; MDD, major depressive disorder; MES, maximal electroshock; NaSSA, noradrenaline and specific serotonergic antidepressant; NDRI, noradrenaline and dopamine reuptake inhibitor; NRI, noradrenaline reuptake inhibitor; PTZ, pentylenetetrazol; PWE, people with epilepsy; SARI, serotonin-2 receptor antagonist and reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; sz, seizure; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant; WAG-Rij, Wistar Albino Glaxo rats from Rijswijk

Introduction

Epilepsy is a common group of neurological disorders whose hallmark is unprovoked seizures (Engel and Pedley, 2007; Berg and Scheffer, 2011). Seizures can be distressing, harmful and even fatal, but an additional and no less significant consequence is the associated comorbidities of epilepsy, which contribute greatly to disability and impaired quality of life. While these can include physical and cognitive impairments as well as adverse effects of antiepileptic drugs (AEDs), it is the psychiatric disorders of several kinds that constitute a large proportion of the burden of comorbidity in epilepsy

(Gaitatzis *et al.*, 2004; Hesdorffer and Krishnamoorthy, 2011). When these psychopathologies, such as depression, are recognized, they are generally treated with antidepressant pharmacotherapy – drugs that have the potential to interfere not only with their target syndromes but also to impact the epilepsy. The mechanisms underlying this interaction will have major implications for the treatment of both epilepsy and comorbid psychiatric disorders.

This review will focus on depressive and anxiety syndromes in epilepsy, the two main sets of disorders for which antidepressants are prescribed (for convenience, the term 'antidepressant' will be employed, although these medications are also used for anxiety and other disorders). Before examining the question that is the focus of this paper, it is useful to set the scene by briefly outlining the definitions and varieties of epilepsy, depression and anxiety and the epidemiological scale of the problem. We will also discuss the natural history and consequences of comorbid anxiety and depression in epilepsy and current theories about their causation. The management of depressive and anxiety disorders in epilepsy is then discussed broadly, before focusing on antidepressant medications – their classes and modes of action.

A key issue structuring this paper is that antidepressants may affect epilepsy in two general ways: via short-term effects on excitability (e.g. seizure threshold, seizure frequency) and via effects on the longer-term neurobiological processes that underlie the epileptic state. First-generation antidepressants, notably tricyclic antidepressants (TCAs), were quickly recognized to have the capacity to trigger seizures in non-epileptic patients (Preskorn and Fast, 1992) (Wroblewski *et al.*, 1990) and to aggravate preexisting epilepsy (Pisani *et al.*, 1999). This was corroborated by *in vivo* (reviewed in (Trimble, 1978) and *in vitro* (Luchins *et al.*, 1984) experimental electrophysiological studies, and consequently, clinicians became reluctant to prescribe any antidepressant to people with epilepsy (PWE) (Cotterman-Hart, 2010). For these and other reasons, many depressed PWE remained – and still remain – either undertreated or completely untreated for their mood disorder. However, a growing body of evidence suggests that newer ('second generation') antidepressants have markedly less effect on excitability and indeed may potentially lead to improvements in epilepsy severity. Considerable effort has been expended improving the detection, diagnosis and treatment of depression (and anxiety) in PWE. Some have proposed that the evidence is now sufficient to conduct clinical trials of the efficacy of antidepressants in improving *epilepsy* endpoints (Favale *et al.*, 1995; 2003), as opposed to solely measuring depression and anxiety endpoints. Whilst the evidence to date is promising, there remain grounds for caution and a need for further, focused research.

Epilepsy: definition and prevalence

The formal definitions of 'seizure' and 'epilepsy' are complex and controversial (Berg *et al.*, 2010); however, a seizure is generally defined as 'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain' (Fisher *et al.*, 2005); and epilepsy is considered 'a group of neurologic conditions, the fundamental characteristics of which are recurrent, usually unprovoked, epileptic seizures' (Engel and Pedley, 2008). An alternative definition of epilepsy, encompassing aspects of the associated comorbidities has been proposed: 'a chronic condition of the brain characterized by an enduring propensity to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition' (Fisher *et al.*, 2005). Current terminology classifies epilepsies as focal or generalized with genetic, structural/metabolic or unknown origins (Berg and Scheffer, 2011), with specific clinical manifestations of seizures determined by the brain structures affected by the abnormal neuronal firing pattern. Collectively, the epilepsies constitute a common group of disorders, with an incidence in developed countries of about 80 per 100 000 persons year^{-1} and a point prevalence of 1–10 cases per 1000 persons (Banerjee *et al.*, 2009; Shorvon, 2010), with the highest incidences observed in children and the elderly.

Epilepsy and its comorbidities

Although recurrent unprovoked seizures are the hallmark of the disorder and can be distressing, harmful and even fatal, the associated comorbidities contribute greatly to disability and impaired quality of life. This can include somatic comorbidities (e.g. cardiac and respiratory disorders) (Gaitatzis *et al.*, 2012), physical impairments such as injury (e.g. burns, fractures), adverse effects of AEDs and impaired fertility in addition to cognitive impairments. Mortality is elevated due to injury, suicide, sudden unexpected death in epilepsy (SUDEP) and underlying diseases that may also give rise to seizures and some epilepsies (e.g. brain tumours). A large proportion of the burden of comorbidity is related to psychiatric disorders (Gaitatzis *et al.*, 2004; Hesdorffer and Krishnamoorthy, 2011; Ottman *et al.*, 2011). The importance of these problems was highlighted by the National Institute of Health Epilepsy Research Benchmarks, which nominated the comorbidities of epilepsy, including prominently psychiatric comorbidities, as priority research areas (Kelley *et al.*, 2009). An important development is depression screening of epilepsy patients. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a six-item scale for use in epilepsy populations (Gilliam *et al.*, 2006; Friedman *et al.*, 2009). Validated in tertiary centres, its properties are as yet unknown in community based epilepsy samples with lower depression prevalence.

Descriptive epidemiology of depressive and anxiety disorders in epilepsy

The most common psychiatric comorbidities in epilepsy include depression, anxiety, attention-deficit hyperactivity disorder and psychoses (Gaitatzis *et al.*, 2004; Hesdorffer and Krishnamoorthy, 2011). For anxiety and depression, rates of these disorders in most community and clinic-based studies are clearly elevated above the general population and often similar to or greater than rates for anxiety and depression associated with other chronic illnesses (for depression, see McLaughlin *et al.*, 2008; Fuller-Thomson and Brennenstuhl,

2009; for anxiety disorders, see Mensah *et al.*, 2007; Kanner, 2011a; for an omnibus study of psychiatric comorbidity, see Tellez-Zenteno *et al.*, 2007). Depression is common in newly presenting patients with epilepsy (e.g. (Panelli *et al.*, 2007; Velissaris *et al.*, 2009) and indeed may precede epilepsy onset and constitute a risk factor for it (Hesdorffer *et al.*, 2012, and see discussion below).

Depression can take several forms: major depressive disorder (MDD), dysthymic disorder, adjustment disorder and depressive phases of bipolar disorder. Debate continues about the validity of 'interictal dysphoric disorder', a depressive-like disorder suggested to be specific to epilepsy but argued by others to be a form of dysthymic disorder (Mula *et al.*, 2010). In addition, depressive symptoms may occur before, during or after a seizure. Many studies have shown associations of comorbid depression with impaired quality of life, greater cognitive deficits and greater health care utilization (Lacey *et al.*, 2009). Indeed, in some studies, depression is a greater predictor of impaired quality of life than epilepsy-related variables, such as illness duration or seizure frequency (Kanner, 2009; Kanner *et al.*, 2010). Depression is a strong risk factor for suicide and a possible risk factor for SUDEP (Ridsdale *et al.*, 2011). Compared with depression, anxiety disorders have until recently been somewhat neglected in epilepsy. However, they have shown to be highly prevalent, often more so than depression, and potentially linked to many of the same adverse consequences as depression (Kanner, 2011a). Anxiety disorder can take several forms, including generalized anxiety or panic, and probably constitute a risk factor for subsequent depression as they do in non-epileptic persons. Given their high prevalence and adverse consequences, management of depressive and anxiety symptoms and syndromes in PWE should be an essential part of epilepsy management and routinely available in services that treat PWE (Barry *et al.*, 2008).

Causation of depressive and anxiety disorders in epilepsy

These affective disturbances tend to be considered either as understandable psychological reaction to the stresses and challenges of living with epilepsy; or as neurobiological epiphenomena of the epileptic brain (Salzberg, 2011). In addition, research interest has focused on two other 'causal arrows': not only may psychiatric disturbance result from epilepsy (via psychological and/or neurobiological pathways), but (i) a psychiatric disorder, notably depression, may also contribute to the causation of epilepsy, and (ii) shared causal factors (e.g. genes, traumatic brain injury, early life stress) may give rise to both psychiatric illness and epilepsy.

Much depression/anxiety research in the epilepsy field is 'either/or' – either psychosocial or neurobiological – and lacks a longitudinal perspective. Present-day general (non-epilepsy associated) depression research is biopsychosocial in nature, integrating insights from genetics, epidemiology, psychology and neurobiology, operating within a diathesis–stress framework (Hoppe and Elger, 2011), and adopts a lifespan perspective (Colman and Ataullahjan, 2010). The same pertains to anxiety disorders. The causation of depression and anxiety disorders is a multistage process with origins in early life; and, after onset of the disorder, there is a very high chance of recurrence throughout the lifespan (Colman and Ataullahjan, 2010). Recently, there have been calls for these perspectives to be adopted more fully in the epilepsy field (Hermann *et al.*, 2008; Hermann and Jacoby, 2009).

Although some good-quality studies have shown associations between factors such as seizure frequency and rates of anxiety and depression, in general, neurological features of epilepsy have been somewhat inconsistent predictors of psychopathology: factors such as age of onset; type, frequency and severity of seizures; epilepsy syndrome (focal or generalized); anatomical location and laterality of focus have all been examined in many studies with often contradictory results (Adams *et al.*, 2008; Filho *et al.*, 2008; Asmussen *et al.*, 2009; Babu *et al.*, 2009; Desai *et al.*, 2010) (for detailed reviews of this extensive and complex literature, see Hoppe and Elger, 2011; Lin *et al.*, 2012). Duration of epilepsy is associated with severity of depression irrespective of epilepsy variables such as seizure type or frequency or EEG alterations (Robertson *et al.*, 1987). The concept of a particular association of psychiatric comorbidity with limbic forms of epilepsy has progressively been eroded by evidence of elevated rates of such disorder in generalized and extra-temporal focal epilepsies (Adams *et al.*, 2008). In part, the concept of a special link with temporal lobe epilepsy arose due to a preponderance of studies of patients in tertiary epilepsy centres, often those being assessed for epilepsy surgery. In contrast to neurological factors, psychosocial factors such as life stress, coping style, social support, perceived stigma and personality have been more consistent predictors (Hermann *et al.*, 2000).

Neurobiologically oriented studies have been more informative, employing structural (Briellmann *et al.*, 2007; Paparrigopoulos *et al.*, 2008; Elst *et al.*, 2009; Salgado *et al.*, 2010; Finegersh *et al.*, 2011; Labate *et al.*, 2011) or functional imaging (Gilliam *et al.*, 2007; Hasler *et al.*, 2007; Bonelli *et al.*, 2009; Assem-Hilger *et al.*, 2010) or both (Richardson *et al.*, 2007; Theodore *et al.*, 2007; Lothe *et al.*, 2008) and, where available, histopathological or molecular pathological study of excised temporal lobe tissue (Frisch *et al.*, 2009). The most consistent findings have been in mesial temporal lobe epilepsy, with suggestions of enlarged amygdalae, diminished hippocampal and neocortical volumes, the latter in both temporal and extra-temporal cortex; diminished $5HT_{1A}$ receptor binding in the hippocampus, and possibly raphe nuclei, insula and cingulate gyrus (Hasler *et al.*, 2007); and a correlation between depression and degree of hippocampal abnormality on ^{1}H-magnetic resonance spectroscopy imaging (Gilliam *et al.*, 2007). Most such studies are cross-sectional, thus unable to determine causality, but the association of depression with diminished extra-temporal cortical thickness (Salgado *et al.*, 2010) is important, as such thinning is found in both ordinary (non-epilepsy-associated) depression and in mesial temporal lobe epilepsy (Labate *et al.*, 2011).

Antiepileptic drugs and psychiatric comorbidities

AEDs have a range of beneficial and adverse psychotropic effects and some are effective as treatments for mania and

bipolar depression and as mood stabilizers in bipolar and schizoaffective disorder (Schmitz, 2011). Patients commonly believe that their AED treatment contributes to their mood-related symptomatology, however, establishing the causal role of any particular AED with regard to an affective symptom is complex, as it may be confounded by type of epilepsy, other co-occurring medication exposures, pre-existing psychopathology, cognitive deficits, the impact on seizure activity (e.g. a marked reduction in seizures may have either beneficial or adverse effects on mood) and pharmacokinetic effects. Also, the characterization of psychological symptoms is often poor: for example, many studies record 'agitation' and 'irritability', ill-defined symptoms that may stem from anxiety or other causes; similarly 'apathy' or 'tiredness' may stem from depression or other causes. However, AEDs thought to cause depressive symptoms and syndromes include carbamazepine, benzodiazepines (clobazam, clonazepam), lamotrigine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, vigabatrin and zonisamide (Mula and Monaco, 2009a; Schmitz, 2011); while levetiracetam, lamotrigine, pregabalin and tiagabine have been linked to anxiety symptoms (Mula and Monaco, 2009a; Schmitz, 2011). Furthermore, a recent meta-analysis has linked AED use with increased suicide risk (FDA, 2008). Despite the aforementioned caveats for linking AED use to any psychopathology, and the methodological issues associated with the meta-analysis (see discussion in Fountoulakis *et al.*, 2012), this report prompted the US Food and Drugs Administration to publish a warning encompassing all AEDs pertaining to this increased risk. This serves to highlight the seriousness and complexities of psychiatric problems associated with AED use.

A bidirectional relationship between epilepsy and psychiatric disorders

The 'causal arrows' considered so far run from epilepsy to psychopathology via various neurobiological pathways including AED exposure and psychosocial effects. However, several lines of evidence suggest a bidirectional relationship between epilepsy and psychiatric disorders and the possibility of shared factors giving rise to both epilepsy and psychiatric disorders (Kanner, 2011b).

First, several AEDs are efficacious for both epilepsy and mood disorders: valproate, carbamazepine and lamotrigine are effective mood stabilizers in bipolar and schizoaffective disorders, with some evidence that topiramate and levetiracetam may also have a role; and lamotrigine has efficacy in treating bipolar depression. Second, epidemiological evidence has emerged that depression is a risk factor for subsequent onset of epilepsy (Forsgren and Nystrom, 1990; Hesdorffer *et al.*, 2000; Nilsson *et al.*, 2003; Hesdorffer *et al.*, 2006; Hesdorffer *et al.*, 2012); and that maternal mood disorder is a risk factor for epilepsy in offspring (Morgan *et al.*, 2012). Third, in most animal epilepsy models, affective disturbance is present, measured by standard tests of anxiety- and depressive-like behaviour. This applies to models of acquired epilepsy, such as electrical kindling (Adamec and Shallow, 2000; Kalynchuk, 2000; Post, 2002; Mazarati *et al.*, 2007), post-status epilepticus (Groticke *et al.*, 2007; 2008; Koh *et al.*, 2007; Mazarati *et al.*, 2008; Muller *et al.*, 2009a,b) and febrile seizure (Mesquita *et al.*, 2006) models; models of genetically determined epilepsy such as Genetically Epilepsy Prone Rats (GEPR) (Jobe and Browning, 2007), Genetic Absence Epilepsy Rats from Strasbourg (GAERS) (Jones *et al.*, 2008b; 2010; Bouilleret *et al.*, 2009), Wistar Albino Glaxo rats from Rijswijk (WAG-Rij) (Sarkisova and van Luijtelaar, 2011) and posttraumatic epilepsy models (Jones *et al.*, 2008a) amongst others. Early life psychosocial exposures have also been shown to contribute to the development of epilepsy, for example maternal separation (Salzberg *et al.*, 2007; Jones *et al.*, 2009; Kumar *et al.*, 2011) and cross-fostering (Gilby *et al.*, 2009) models, as well as leading to alterations in cellular electrophysiology (Ali *et al.*, 2011). Fourth, disturbances in several key neurotransmitter systems are implicated in epilepsies and depression, notably serotonergic, noradrenergic, GABAergic and glutamatergic systems (Jobe *et al.*, 1999; Olsen *et al.*, 1999; Cotter *et al.*, 2002; Kanner and Balabanov, 2002; Jobe, 2003; Bagdy *et al.*, 2007). Finally, in several studies, prior depression (or psychopathology more generally) is a predictor of treatment resistance, both to AEDs (Hitiris *et al.*, 2007; Petrovski *et al.*, 2010) or to epilepsy surgery (Kanner *et al.*, 2009; Metternich *et al.*, 2009), although a recent study of a temporal lobectomy series failed to find this association (Adams *et al.*, 2012). Other commonalities in the neurobiology of epilepsy and depression/anxiety are discussed below, as they relate to the mechanisms of action of antidepressants.

Current treatment of anxiety and depression in epilepsy

For both depressive and anxiety disorders, the main effective treatments available at present are various psychotherapies, pharmacotherapies and their combination (other treatments employed for very severe or treatment-resistant illness will not be considered here, e.g. electroconvulsive therapy, psychosurgery, deep brain stimulation and transcranial magnetic stimulation). There is good evidence for the efficacy of psychotherapies in depression, with probable superiority to antidepressants in reducing relapse; there is also growing evidence specifically for depression in epilepsy (Ciechanowski *et al.*, 2010; Thompson *et al.*, 2010; Walker *et al.*, 2010). Interestingly, vagal nerve stimulation has shown efficacy for both treatment-resistant epilepsy and treatment-resistant depression, suggesting shared neurobiological factors in their causation and/or treatment (Furmaga *et al.*, 2012).

The various points at which antidepressant medication may be introduced during the course of epileptogenesis are shown in Figure 1. The principles of treatment selection are complex and beyond the scope of this review: many factors need to be taken into account such as the specific syndrome, past episodes of illness and past treatment response, physical comorbidities, other medications and risk of drug interactions, risk of suicide, suitability for psychotherapy, as well as cost and patient preferences and attitudes and beliefs regarding treatment options. However, an important principle is

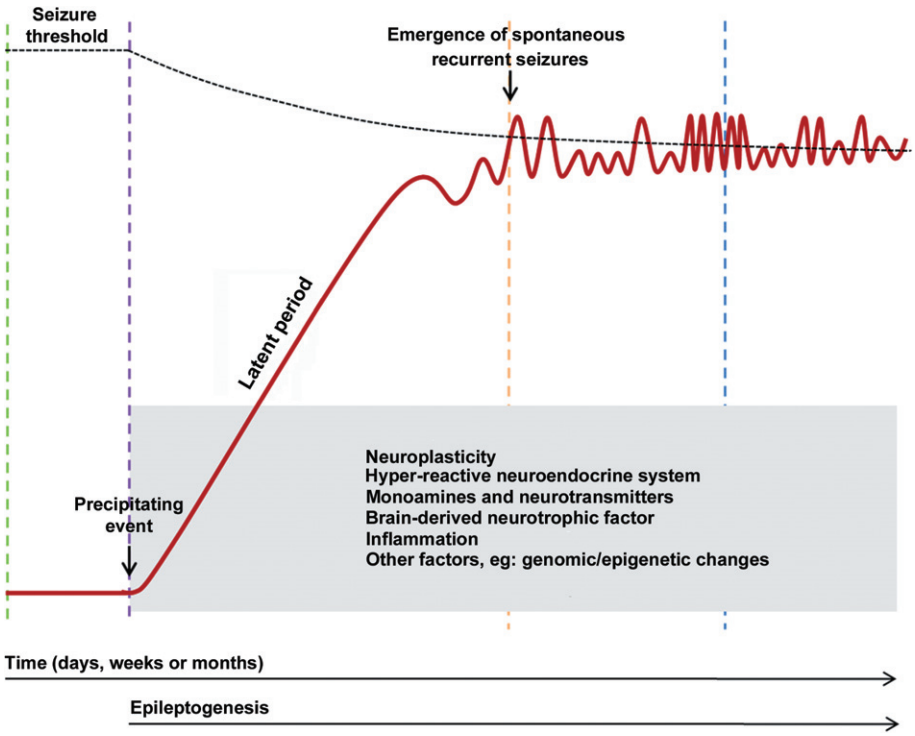

Figure 1

The time course of epileptogenesis and the typical stages at which antidepressants may be clinically introduced. Neurobiological mechanisms involved in epileptogenesis are indicated in the grey box, a period that includes the time after the precipitating event to the latent period and the emergence of spontaneous, recurrent seizures. While this process is typical of epileptogenesis following an acquired injury, similar alterations following this time course can also occur with genetic epilepsies. At points before or during epileptogenesis, antidepressant medication may be initiated, indicated by the dashed vertical lines: green, prior to epilepsy onset; purple, the period immediately after a precipitating event; orange, the period around when seizures emerge; blue, during active epilepsy. At each of the points, antidepressants may impact on the different neurobiological alterations occurring in epileptogenesis, potentially influencing disease course. Figure modified from Scharfman (2007).

the considerable evidence for additive or synergistic effects of combined psychotherapy and medication for treatment of several disorders, both for initial treatment and prevention of relapse (Busch and Sandberg, 2012). This has been demonstrated recently in a mouse model (Karpova *et al.*, 2011) where a combination of fear-extinction training and fluoxetine was effective in erasing conditioned fear, where each treatment separately was ineffective.

As the evidence base for anxiety and depression treatments in PWE is exceptionally small, treatment is largely informed by evidence from non-epilepsy patients (for reviews, including treatment guidelines see (Barry *et al.*, 2008; Mula *et al.*, 2008; Mula and Schmitz, 2009b; Noe *et al.*, 2011; Perr and Ettinger, 2011; Kanner *et al.*, 2012). Psychological interventions for depression and/or anxiety in PWE have been trialled in recent years (Ciechanowski *et al.*, 2010; Walker *et al.*, 2010; Macrodimitris *et al.*, 2011), but combined therapies – psychotherapy with medication – have not yet been reported.

Antidepressants

The focus of this review will remain on the antidepressants most commonly prescribed to PWE suffering from depression and/or anxiety; principally selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI) and related medications. These compounds are also useful for the treatment of other disorders, including chronic pain, sleep disorders, attention-deficit hyperactivity disorder and eating disorders. Table 1 summarizes the main antidepressants available for use in patients with depression and anxiety disorders, using the conventional classification based on synaptic actions. Whilst various other drugs, such as antipsychotics, ketamine and mood stabilizers (e.g. lithium, valproate, carbamazepine), have been shown to have antidepressant and sometimes anti-anxiety properties, they will not be discussed further, nor will the scores of novel medications at various stages of development (Stahl, 2008); the focus here is on established medications in common clinical usage.

Second-generation antidepressants: SSRIs and SNRIs

Due to better tolerability, with reduced side effects and relative safety in overdose compared with TCAs, SSRIs and SNRIs are the first-line drugs for the treatment of depression, especially in epilepsy. These drugs selectively inhibit serotonin reuptake at the neuronal presynaptic membrane by blocking

Table 1

Antidepressants in current clinical use

Drug class	Examples in clinical use	Proposed mechanism of action	References to studies of use in patients or epilepsy models
Selective serotonin reuptake inhibitor (SSRIs)	Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline	Blockade of SERT, plus some with additional pharmacological actions	Favale *et al.* (1995); Kanner *et al.* (2000); Specchio *et al.* (2004)
Serotonin and noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine, Desvenlafaxine, Duloxetine	Selective SERT and NET blockade	Santos *et al.* (2002); Ahern *et al.* (2006); Borowicz *et al.* (2011)
Tricyclics (TCAs)	Imipramine, Desipramine, Doxepin, Dothiepin, Amoxapine	Blockade of SERT and NET, also acting on histaminergic and cholinergic receptors. Negligible DAT affinity	Dessain *et al.* (1986); Preskorn and Fast (1992)
Monoamine oxidase inhibitor (MAOIs), *reversible*	Moclobemide	Reversible inhibition of MAO-A (and others MAO-B also)	Trimble (1978); Bonnet (2003); Krishnan (2007)
Monoamine oxidase inhibitor (MAOIs), *irreversible*	Tranylcypromine, Phenelzine	Irreversible inhibition of MAO-A and MAO-B	Pisani *et al.* (2002)
Noradrenaline reuptake inhibitors (NRIs)	Reboxetine	Blockade of NET	Kuhn *et al.* (2003)
Noradrenaline dopamine reuptake inhibitor (NDRI)	Bupropion	Not well defined, but shown to be a noradrenaline and dopamine reuptake inhibitor	Settle *et al.* (1999) Mainie *et al.* (2001)
Serotonin-2 receptor antagonist and reuptake inhibitors (SARIs)	Trazodone, Nefazodone	Antagonist of 5-HT_{2A} receptor and blockade of SERT	Vanpee *et al.* (1999)
Noradrenaline and specific serotonergic antidepressant (NaSSA)	Mirtazapine	Blockade of 5-HT_2 receptors, 5-HT_3, H_1 and α_2 adrenergic receptor antagonist	Kuhn *et al.* (2003)
Others	Agomelatine	Melatonergic (MT_1 and MT_2) receptor agonist, $5HT_{2C}$ antagonist	No reported use in PWE

DAT, dopamine transporter; NET, norepinephrine (noradrenaline) transporter; SERT, serotonin transporter.

the serotonin reuptake transporter, or in the case of SNRIs, the noradrenaline transporter as well, increasing serotonin and/or noradrenaline levels in the synapse. While being mostly selective in this action, there are also some effects on muscarinic and α-adrenergic receptors and on dopamine reuptake.

While considered safe for use in epilepsy, a dose-dependent increase in seizures has also been shown in overdose (Isbister *et al.*, 2004). Furthermore, consideration of the pharmacokinetic interaction with AEDs is also important when prescribing these drugs to PWE. Some AEDs have been shown to increase clearance of antidepressants (e.g. carbamazepine), while some antidepressants can inhibit clearance of AEDs through interaction with the CYP-450 hepatic enzyme system (summarized in Barry *et al.*, 2008).

Classifying antidepressants according to their synaptic targets is clinically useful, giving better understanding of the potential side effects and toxicity. However, direct activity at these pharmacological targets has long been recognized to not adequately explain their actions (discussed in Nestler *et al.*, 2001). The acute increases in synaptic monoamine levels occurring as a consequence of reuptake inhibition are at odds with the timeframe of 2–3 weeks required for clinical antidepressant action and even longer for efficacy in anxiety disorders. Longer-term adaptations to antidepressants, mediated via second-messenger systems and entailing changes in gene expression and protein translation lead to downstream effects on neurogenesis and other forms of neuroplasticity, the neuroendocrine system [notably the hypothalamo–pituitary–adrenal (HPA) axis], other neurotransmitter systems and inflammatory pathways. Much evidence also implicates both neurotrophins, such as BDNF, and epigenetic mechanisms in these diverse actions. These various pathways and mechanisms become relevant when attempting to identify the mechanisms by which these compounds may also influence epilepsy and are discussed later. First, we summarize the human and experimental literature documenting the effects of antidepressants on seizure and epilepsy outcomes.

Studies of antidepressants in epilepsy: humans

Since the early reports of seizures as side effects of first generational antidepressants (such as TCAs – (Preskorn and Fast,

Table 2

Effects of antidepressants in patients with epilepsy

Study group	Antidepressants	Follow up	Seizure frequency in treatment group	Reference
9 PWE	FLX	3 months	4 Px increase in seizure frequency by >50%; 5 Px not increased	Gigli *et al.* (1994)
36 PWE and MDD	SRT, FLX	1 year	2 Px increase in seizure frequency; 34 Px not increased (number of Px with *reduced* seizures not mentioned)	Thome-Souza *et al.* (2007)
100 PWE and depression or OCD	SRT	1 year	6 Px increase in seizure frequency; 94 Px not increased (number of Px with *reduced* seizures not mentioned)	Kanner *et al.* (2000)
39 PWE and depression	CIT	4 months	2 Px had 50% increase in seizures; 37 Px with 50% decrease in seizures	Specchio *et al.* (2004)
11 PWE	CIT	8–10 months	All Px showed improvements: 64.1% mean reduction in seizure frequency	Favale *et al.* (2003)
17 PWE	FLX	14 months	Seizures disappeared in 6 Px; in others, seizure frequency reduced by 30%	Favale *et al.* (1995)
43 PWE and HAMD score >15	CIT	2 months	No change in seizure frequency	Hovorka *et al.* (2000)
75 PWE and HAMD score >15	MIR, CIT, REB	7.5 months	No change in seizure frequency	Kuhn *et al.* (2003)
28 PWE	FLV	29–444 days	No change in seizure frequency	Harmant *et al.* (1990)
121 PWE	Various 1st and 2nd gen. drugs	1 year	No change in seizure frequency compared to non-treated Px	Okazaki *et al.* (2011)

Patient drop outs not included in sample sizes.
CIT, citalopram; FLV, fluvoxamine; FLX, fluoxetine; HAMD, hamilton depression rating scale; MDD, major depressive disorder; MIR, mirtazepine; OCD, obsessive compulsive disorder; PWE, people with epilepsy; Px, patients; REB, reboxetine; SRT, sertraline.

1992; Salzberg and Vajda, 2001), more recent reports have revisited this issue, focusing on newer generation drugs. These clinical studies have largely investigated effects of antidepressants in PWE on seizure frequency, but have not addressed whether antidepressants have influence on the processes associated with epileptogenesis. Studies investigating the effects of SSRI or SNRI treatment in PWE are summarized in Table 2. In these 10 studies, all patients received antidepressants adjunct to AED therapy, whether to treat the comorbid depressive symptoms or to assess the antiepileptic potential of the antidepressant. In all but one of the studies (see Kanner *et al.*, 2000), patients were monitored for the occurrence of seizures in the months before and then during antidepressant treatment.

With long-term SSRI/SNRI antidepressant treatment (1 month to approximately 15 months), the overall group effects in these studies suggest that there is no worsening in seizure frequency (Harmant *et al.*, 1990; Gigli *et al.*, 1994; Hovorka *et al.*, 2000; Kanner *et al.*, 2000; Kuhn *et al.*, 2003; Thome-Souza *et al.*, 2007; Okazaki *et al.*, 2011). Moreover, in several of the studies, improvements in seizure outcomes are seen, with some patients experiencing dramatic and complete seizure freedom during AD treatment (Favale *et al.*, 1995; 2003; Specchio *et al.*, 2004). It should be noted that some individuals in these studies experienced a worsening of seizure frequency (Gigli *et al.*, 1994; Kanner *et al.*, 2000; Specchio *et al.*, 2004), but these were generally rare occurrences, and could be reversed by either increasing the AED medication, or removing the antidepressant. Nevertheless, this should be taken into account when considering these studies. It should also be noted that in most studies that assessed features of depression, these improved in a large proportion of the patients, which should also be considered as an important outcome.

As with many clinical studies, considerable limitations exist when interpreting these effects of antidepressants in PWE. These limitations are particularly pertinent when regarding the studies in which SSRIs either did not adversely affect seizures (Gigli *et al.*, 1994), or reduced seizure frequency (Favale *et al.*, 1995; 2003), which were very small studies, open-labelled, and contained short time periods of treatment and seizure analysis. Overall, there have been no double-blind, randomized controlled studies; most of the studies have been small and on highly selected patient populations from epilepsy clinics or following epilepsy surgery, and with few longitudinal, follow-up studies. Furthermore, assessment of antidepressants on seizure outcomes may be hindered by other factors, such as AED (or antidepressant) compliance, stress or insomnia. Also, all but one study assessed seizures before and after antidepressant treatment, which could be confounded by fluctuations in seizure frequency – common throughout the course of the illness. Case-control study designs should be employed, where a proportion of patients receive no active treatment (see Kanner *et al.*, 2000).

Of note, an influential study by Alper *et al.* (2007) reviewed the effects of antidepressant drugs on seizure inci-

dence in ~75 000 non-epileptic patients in phase II and III clinical trials of depression treatment. The study found a significantly decreased incidence of seizures occurring in depressed patients treated with antidepressants compared to those treated with placebo (Alper *et al.*, 2007). Despite the fact that patients with known epilepsy would have been excluded from such clinical trials, it is interesting to note that the rate of spontaneous seizures in the depressed patients in these trials was considerably above known population rates. Although not performed in PWE, this report strongly suggests an overall anti-seizure effect of antidepressants at therapeutic doses, consistent with the findings from studies in PWE (Table 2).

To date, there have been no clinical studies that have investigated whether antidepressant treatment has disease-modifying effects on the epilepsy itself (as opposed to anti-seizure effects). Undertaking such a study would be logistically difficult, requiring long-term treatment and follow-up, appropriately matched placebo-treated controls and the need to address various manifestation of epilepsy progression, such as seizure frequency, AED resistance, neuropsychiatric and neurocognitive deficits and structural brain changes. This can be more readily addressed in appropriate animal models, where long-term follow-up and assessment of epileptic outcomes, in addition to behavioural, structural and functional changes can be achieved in a shorter time frame and with greater control of experimental settings.

Studies of antidepressants in epilepsy: animal models

Both genetic and acquired models of epilepsy are valuable tools for assessing the biological processes and modulators of epilepsy development and progression. Many of these models accurately recapitulate the human disease and are appropriately used to assess drug response and efficacy on seizures and comorbidities. As mentioned above, a wide variety of animal models of epilepsy, both with acquired and genetic aetiology, also exhibit behaviours relevant to the psychiatric comorbidities present in PWE. The presence of the psychiatric comorbidities in both humans and in animal models of epilepsy suggests shared neurobiological mechanisms may be at play. However, how antidepressants affect these mechanisms and the disorders themselves is unclear and needs to be resolved.

There have been several studies investigating the effects of antidepressants on seizure occurrence in animal models. A recent review focusing on SSRIs concluded that, overall, treatment with this form of antidepressant exerts anticonvulsant effects in animal models of seizures/epilepsy (Igelstrom, 2012). Previous studies in animal models have shown that TCAs (Koella *et al.*, 1979; Preskorn and Fast, 1992; Ago *et al.*, 2006, 2007) increase seizure susceptibility, in line with the data from human studies showing a similar increase in seizure occurrence during TCA treatment (Preskorn and Fast, 1992). Similar pro-seizure effects have been reported for bupropion, a noradrenaline-dopamine reuptake inhibitor (Settle *et al.*, 1999). The studies of all of the newer generation antidepressants on seizure outcomes in animal models of epilepsy are summarized in Table 3. Although there are seven studies reporting proconvulsant activity of SSRIs exclusively tested using acute seizure assessments, the majority of studies, which include models of both acute seizures and chronic epilepsy, indicate that overall, SSRIs and SNRIs exert either beneficial effects (25 studies) or are without influence (19 studies) on seizure outcomes. This suggests that the effects wrought by antidepressants on seizures are dependant upon the model used: these drugs are generally beneficial in the more clinically relevant models of chronic partial epilepsy, such as the post-status epilepticus, GEPRs, El mice and limbic kindling models, but can be detrimental in models of acute seizures, including pentylenetetrazol (PTZ)-, lidocaine- or fluorothyl-induced seizures.

Although more labour-intensive, models of chronic epilepsy are the most appropriate to study effects of drugs. The post-status epilepticus model is one of the most widely used and well-validated chronic models of mTLE (Morimoto *et al.*, 2004). Using this model, Hernandez *et al.* (2002) found that five days fluoxetine treatment inhibited spontaneous recurrent seizures following pilocarpine-induced status epilepticus (Hernandez *et al.*, 2002), while in the same model, Mazarati *et al.* (2008) found no differences in spontaneous recurrent seizures following 10 days of fluoxetine treatment (Mazarati *et al.*, 2008). In the post-kainic acid-induced status epilepticus model, Vermoesen *et al.* (2012) investigated the effects of 4 days of citalopram treatment, finding that citalopram reduced seizure frequency and cumulative seizure duration, without affecting seizure severity (Vermoesen *et al.*, 2012). These strong studies suggest SSRIs are able to improve seizure outcomes when used in chronic epilepsy models, although the period of SSRI treatment, from 3–10 days, is relatively brief.

The strength of the collective data suggesting that antidepressants have no effect on seizures and may even be anticonvulsant is that the evidence is derived from a wide variety of models including both chemoconvulsant and electrically induced seizures, genetic models of epilepsy and also the use of different animal species. However, limitations to the majority of studies also exist: (i) many utilize acute seizure tests, such as the PTZ and maximal electroshock (MES) models, in otherwise non-epileptic animals. This is very different situation to the pathological circuits associated with truly epileptic brains, and so drugs may well have contrasting effects in such conditions. Only three studies have investigated long-term seizure outcomes in chronically epileptic rats following antidepressant treatment (Hernandez *et al.*, 2002; Mazarati *et al.*, 2008; Vermoesen *et al.*, 2012) – see description above. (ii) Many of the models do not exhibit behavioural abnormalities indicative of psychopathology in humans, and so an examination of effects on depression-related outcomes is tenuous. (iii) There is large variety in experimental design relating to the dose and timing of injection of the antidepressant relative to seizure susceptibility testing, making collective interpretation difficult. (iv) In many studies, antidepressants were administered as a single dose, and this does not mimic the clinical situation where several weeks of treatment are required for the beneficial therapeutic effect of antidepressants to manifest in patients. Indeed, only about half of all the studies (16 of 36) reviewed in Table 3 incorporate a chronic treatment arm (defined as more than 2 days of ongoing treatment). Similarly absent in the experimental

Table 3

Studies of antidepressant administration in animal models of seizures and epilepsy

Model	Species	Drug	Dose (mg kg^{-1})	Study protocol	Seizure outcome measures	Reference
Antidepressants were found to be proconvulsant						
PTZ	Mouse	CIT	25, 50	Injection 30 min prior to sz test	Behavioural threshold	Payandemehr *et al.* (2012)*
PTZ	Rat	FLX	10	Injection 1 h prior to sz test	Severity	Zienowicz *et al.* (2005)
PTZ	Rat	FLX	10	Sz tested after 21 days admin.	Behavioural threshold	Ferrero *et al.* (2005)
PTZ	Rat	VEN	75–100	Injection 30 min prior to sz test	Severity and latency	Santos *et al.* (2002)
Lidocaine	Mouse	DES, MAP	5–20	Sz tested 2–5 after 5 days admin.	Severity, threshold, frequency	Arai *et al.* (2003)*
Lidocaine	Mouse	CIT	10	Injection 30 min prior to sz test	Frequency	Arai *et al.* (2003)*
Pilocarpine	Mouse	CIT, REB, BUP	15,30,20–40	Injection 30 min prior to sz test	Behavioural threshold	Vermoesen *et al.* (2011)*
Flurothyl	Mouse	SRT, BUP	40,40	Injection 30 min prior to sz test	Latency	Ahern *et al.* (2006)*
Flurothyl	Mouse	REB	20	Sz tested after 21 days admin.	Latency	Ahern *et al.* (2006)*
Antidepressants were found to be anticonvulsant						
MES	Mouse	BUP	15–30	Injection 30 min prior to sz	Behavioural threshold	Tutka *et al.* (2004)*
PTZ	Zebrafish	CIT, REB, BUP	10–300 μM	Injection 1 min prior to sz	Behavioural threshold	Vermoesen *et al.* (2011)*
PTZ	Mouse	REB, BUP	5–10, 10–40	Injection 30 min prior to sz test	Behavioural threshold	Vermoesen *et al.* (2011)*
PTZ	Mouse	FLX	20	Injection 60 min prior to sz test	Survival	Kecskemeti *et al.* (2005)*
PTZ	Mouse	FLX	1–20	Injection 30 min prior to sz test	Behavioural threshold, latency	Ugale *et al.* (2004)
PTZ	Mouse	CIT	0.5, 1	Injection 30 min prior to sz test	Behavioural threshold	Payandemehr *et al.* (2012)*
PTZ	Rat	VEN	25–50	Injection 30 min prior to sz test	Severity and latency	Santos *et al.* (2002)
Pilocarpine	Zebrafish	CIT	10–300 μM	Injection 1 min prior to sz test	Behavioural threshold	Vermoesen *et al.* (2011)*
Pilocarpine	Rat	FLX	20	Once epileptic, drug admin for 5 days, sz assessed for 72 h	SRS	Hernandez *et al.* (2002)
Pilocarpine	Rat	FLX	20	Once epileptic, drug admin for 10 days, sz assessed for 7 days	Behavioural threshold	Mazarati *et al.* (2008)*
Flurothyl	Mouse	REB	20	Sz tested after 21 days admin.	Latency	Ahern *et al.* (2006)*
Focal pilocarpine	Rat	CIT	1 μM	Sz tested over 4 h drug infusion	Severity	Clinckers *et al.* (2004)
Focal bicuculline	Rat	FLX	5–20	Injection 1 h prior to sz test	Frequency, severity	Prendiville and Gale (1993)
Focal bicuculline	Rat	FLX	1.75–7 nM	Injection 15 min prior to sz test	Behavioural threshold	Pasini *et al.* (1992)
Picrotoxin	Mouse	FLX	20	Injection 65 min prior to sz test	Latency	Pericic *et al.* (2005)*
Picrotoxin	Mouse	FLX	20	Sz tested after 5 days admin.	Latency	Pericic *et al.* (2005)*
KA	Mouse	CIT	10	Sz tested after 7 days admin.	Severity	Jaako *et al.* (2011)
KA	Rat	CIT, REB	15, 20–30	Once epileptic, drug admin for 4 days and sz assessed	Frequency, cumulative duration	Vermoesen *et al.* (2012)*
MES	Mouse	VEN	12.5, 25	Injection 30 min prior to sz test	Convulsive threshold	Borowicz *et al.* (2011)*
MES	Mouse	VEN	12.5, 25	Sz tested after 14 days admin.	Convulsive threshold	Borowicz *et al.* (2011)*
MES	Mouse	FLX	10	Injection 60 min prior to sz test	Hind limb extension threshold	Raju *et al.* (1999)*
Ear shock	Mouse	FLX	15–25	Injection 30 min prior to sz test	Hind limb extension threshold	Borowicz *et al.* (2006)*
Hippocampal kindling	Rat	FLX	10 nmol	Injection 15 min prior to sz test	Electrical threshold	Wada *et al.* (1993)

Table 3

Continued

Model	Species	Drug	Dose (mg kg^{-1})	Study protocol	Seizure outcome measures	Reference
Hippocampal kindling	Rat	FLX	10	Sz tested after 21 days admin., 7 days wait, one injection	Electrical threshold^	Wada *et al.* (1995)*
Amygdala kindling	Cat	FLX	2–10	Injection 1–49 h prior to sz test	Electrical threshold	Siegal and Murphy (1979)
GEPR-3 and GEPR-9	Rat	FLX	30	Injection 1–5 h prior to sz test	Severity	Dailey *et al.* (1992)*
GEPR-3 and GEPR-9	Rat	FLX	7–20	Sz tested every 7 days over 28 days admin.	Behavioural threshold	Dailey *et al.* (1992)*
GEPR-9	Rat	FLX	15	Injection 1 h prior to sz test	Severity and latency, behavioural	Yan *et al.* (1994)
El mice	Mouse	CIT	0.01, 0.02, 0.04%#	Sz tested after 14 days admin.	Behavioural threshold	Kabuto *et al.* (1994b)
El mice	Mouse	FLX	10	Sz tested after 3 or 7 days admin.	Behavioural threshold	Richman and Heinrichs (2007)
Antidepressants resulted in no change						
PTZ, KA	Mouse	BUP	5–50	Injection 30 min prior to sz test	Number of convulsions	Tutka *et al.* (2004)*
PTZ, LH	Rat	FLX	10	Injection 1 h prior to sz test	Behavioural threshold	Ferrero *et al.* (2005)*
PTZ, pilocarpine	Mouse	CIT, REB, BUP	various	Injection 30 min prior to sz test	Behavioural threshold	Vermoesen *et al.* (2011)*
PTZ	Mouse	FLX	20	Injection 60 min prior to sz test	Latency	Kecskemeti *et al.* (2005)*
PTZ	Rat	FLX	2.5–20	Injection 30 min prior to sz test	Latency and severity	Ceyhan *et al.* (2005)
Lidocaine	Mouse	DES, MAP	20	Sz tested 5–9 after 5 days admin.	Frequency	Arai *et al.* (2003)*
Lidocaine	Mouse	CIT	10–20	Sz tested after 5 days admin.	Frequency, threshold	Arai *et al.* (2003)*
Pilocarpine	Zebrafish	REB, BUP	10–100	Injection 1 min prior to sz test	Behavioural threshold	Vermoesen *et al.* (2011)*
Pilocarpine	Rat	FLX	20	Once epileptic, drug admin for 10 days, sz assessed for 7 days	Seizure frequency	Mazarati *et al.* (2008)*
Flurothyl	Mouse	VEN, REB	20–40,20	Injection 30 min prior to sz test	Latency	Ahern *et al.* (2006)*
Flurothyl	Mouse	VEN, BUP, SRT	20–40,40,40	Sz tested after 21 days admin.	Latency to first seizure	Ahern *et al.* (2006)*
KA	Mouse	FLX	10–50	Injection 30 min prior to sz test	Severity and duration	Jin *et al.* (2009)
KA	Rat	CIT, REB	5–10, 10	Once epileptic, drug admin for 4 days and sz assessed	Severity and duration	Vermoesen *et al.* (2012)*
MES	Mouse	FLX	10	Sz tested after 21 days admin.	Hind limb extension threshold	Raju *et al.* (1999)*
Ear shock	Mouse	FLX	10	Injection 30 min prior to sz test	Hind limb extension threshold	Borowicz *et al.* (2006)*
Ear shock	Mouse	FLX	7.5–20	Sz tested after 14 days admin.	Hind limb extension threshold	Borowicz *et al.* (2007)
Hippocampal kindling	Rat	FLX	10	Injection 2 h prior to sz test	Threshold and duration	Wada *et al.* (1999)
Hippocampal kindling	Rat	FLX	1,10	Injection 1 h prior to sz test	Electrical threshold	Wada *et al.* (1995)*
EEG	Rat	FLV, CLV	10–30	Drugs infused and seizures assessed at 10 min intervals	Epileptic activity on EEG	Krijzer *et al.* (1984)
GEPR-3	Rat	FLX	3.5, 7.2, 14.1 nmol	Injection 15 min prior to sz test	Severity and latency	Statnick *et al.* (1996)
GEPR-9	Rat	FLX	15	Injection 2 h prior to sz test	Severity and latency	Browning *et al.* (1997)
El mice	Mouse	CIT	80	Sz tested after 14 days admin.	Behavioural threshold	Kabuto *et al.* (1994a)

*Study is repeated within the table; #dietary supplement; ^no difference after 4 weeks.

ADT, afterdischarge threshold; BUP, bupropion; CIT, citalopram; CLV, clovoxamine; DES, desipramine; FLV, fluvoxamine; FLX, fluoxetine; GEPR, genetically epilepsy prone rats; h, hour; KA, kainic acid; LH, learned helplessness; MAP, maprotiline; min, minute; PAR, paroxetine; SRS, spontaneous recurrent seizures (as recorded on EEG); sz, seizure; VEN, venlafaxine.

literature are any studies examining epileptogenesis. Future studies need to address the effects of chronic antidepressant treatment in chronic epilepsy models, incorporating measures of disease progression, as well as effects on seizure propensity. At the current state of play, the evidence suggests that seizure susceptibility can be influenced by antidepressant exposure. Next, we discuss several potential mechanisms that are candidates to mediate these effects.

Shared neurobiological substrates of antidepressant action and epileptogenesis

Understanding the mechanisms by which antidepressants influence epilepsy has not been thoroughly investigated, despite the broad literature on the neurobiological effects of antidepressants, and also of the pathophysiological processes associated with epileptogenesis. Analysing these two bodies of literature reveals several intermediary substrates that have been prominently linked to antidepressant activity and icto/epileptogenic mechanisms. The following section describes in detail these relevant intermediaries, the most prominent being neurogenesis and other forms of neuroplasticity; the HPA axis and glucocorticoids; monoamines and other neurotransmitters; BDNF; and inflammatory processes. Although these candidates are discussed separately, clearly there is an overlap – for example, the role of antidepressants on neurogenesis may be driven by BDNF signalling (Li *et al.*, 2008), and glucocorticoids exert powerful effects on hippocampal neurogenesis (Mirescu and Gould, 2006) and inflammatory processes (Sorrells and Sapolsky, 2007). This list is by no means exhaustive, and other processes, including genetic/genomic and epigenetic mechanisms may equally be important. For instance, ketamine has recently shown promise as an effective antidepressant (Zarate *et al.*, 2006), actions that may be linked to the mTOR pathway (Li *et al.*, 2010), a pathway recently been implicated in a broad range of models of epileptogenesis (Wong, 2010).

Neurogenesis/neuroplasticity

The hippocampus retains significant capacity for neuroplasticity in adult life and is associated with many mood and neurological disorders (Small *et al.*, 2011). Indeed, one of the key features of acquired epilepsy is aberrant hippocampal plasticity, which may result in the generation of hyperexcitable circuitry. Studies in both patients and animal models of temporal lobe epilepsy display a selective pattern of pyramidal cell loss in CA1 and CA3 regions (Corsellis, 1957; Sloviter, 1994a,b), gliosis (Niquet *et al.*, 1994), axonal sprouting (which results in formation of recurrent synapses) (Tauck and Nadler, 1985; Mathern *et al.*, 1998; Buckmaster *et al.*, 2002; Kron *et al.*, 2010) and aberrant migration of granule cells (McCloskey *et al.*, 2006; Scharfman *et al.*, 2007). The hippocampus is also frequently the site of seizure initiation (Babb, 2001). Aberrant hippocampal neuroplasticity is therefore considered to be a prevalent feature of acquired epilepsy and represents a strong candidate mechanism by which antidepressant drugs might interact with disease processes.

In recent years, one of the most widely studied forms of hippocampal neuroplasticity associated with epilepsy has been neurogenesis – the birth and integration of new neurons into the existing hippocampal circuitry. Neurogenesis persists into adulthood in discrete brain regions in both animals (Altman and Das, 1965) and humans (Eriksson *et al.*, 1998), and alterations in neurogenesis are a key feature in both humans and animal models of epilepsy (Parent *et al.*, 2006). Acute seizures stimulate the production of new neurons (Bengzon *et al.*, 1997), whereas dramatically reduced rates in neuronal differentiation have been observed in chronically epileptic rats (Hattiangady *et al.*, 2004; Hattiangady and Shetty, 2010). Following status epilepticus – an extended period of sustained seizures that can result in the development of epilepsy – newly generated neurons migrate ectopically into the dentate hilus region, creating aberrant dendritic connections which may contribute to the generation of epileptic circuitry (Parent *et al.*, 1997; Scharfman *et al.*, 2007; Kron *et al.*, 2010). However, other reports suggest that some of these newly generated neurons play roles that would serve to protect the injured hippocampus from excessive excitability (Jakubs *et al.*, 2006; Murphy *et al.*, 2011), so it is not yet clear how the neurogenic response to seizures impact the development of epilepsy.

Antidepressants, particularly SSRIs, are also reported to increase hippocampal neurogenesis in both humans (Boldrini *et al.*, 2009) and animals (Malberg *et al.*, 2000; Santarelli *et al.*, 2003). Indeed, early reports suggest that this property is critical for antidepressant activity in animal models (Santarelli *et al.*, 2003), although this is still subject to debate (Miller *et al.*, 2008; Zhao *et al.*, 2008; Bessa *et al.*, 2009). Exploration of the components of the 'neuronal differentiation cascade' suggests that antidepressants specifically increase the division of early neural progenitor cells, but not stem cells or neuroblasts (Encinas *et al.*, 2006). Another intriguing property of SSRIs is their ability to reverse the maturation of a significant proportion of dentate granule cells into cells with immature neuronal properties (Kobayashi *et al.*, 2010; Karpova *et al.*, 2011), changes that could result in reduced mossy fibre synaptic facilitation from the dentate gyrus to CA3 region. This could have relevance for the spread of epileptic activity through the hippocampal circuitry. Together, these data describe significant effects of antidepressants on hippocampal neuroplasticity, which may be relevant for the reorganization of this structure during epileptogenesis.

Two studies to date have specifically examined neuroplasticity associated with chemoconvulsant-induced seizures during chronic treatment with the SSRI citalopram. These found that antidepressant treatment reduced levels of reactive gliosis and aberrant cell proliferation (Jaako *et al.*, 2009) and reduced cell death and axonal sprouting (Jaako *et al.*, 2011) induced by the seizures. This suggests that chronic exposure to SSRIs mitigates against the pathological hippocampal circuit remodelling induced by seizures, potentially preventing the onset of epilepsy which occurs after this insult (although this was not explored). However, much remains to be examined with respect to the influence of antidepressants on hippocampal neuroplasticity in the context of epilepsy/epileptogenesis. For instance, how does antidepressant exposure alter the migration, and the electrophysiological phenotype, of newly born neurons following brain insults?

How do existing granule cells exposed to antidepressants respond when challenged with a brain injury? By increasing the number of newborn cells, are antidepressants accelerating or impeding the creation of hyperexcitable circuits following injury? Long-term studies determining the effect of antidepressants on neurogenesis and associated neuroplastic rearrangements in epilepsy are crucial to understand how these drugs may influence epileptogenesis.

Hypothalamo–pituitary–adrenal axis and glucocorticoids

Glucocorticoids are steroid hormones released in circadian and pulsatile rhythms, and also in times of stress. These hormones have many homeostatic functions in the body and also perform specialized actions in the brain related to the function of the amygdala and hippocampus (Joels and Baram, 2009), key structures implicated in both epilepsy and depression. Circulating and stress-induced levels of glucocorticoids are tightly regulated by the HPA axis, which releases glucocorticoids into the circulation. Negative and positive feedback loops incorporating the hippocampus and amygdala further regulate the activity of the HPA axis (Lupien *et al.*, 2009). While HPA axis hyperactivity is one of the most consistent attributes in depressed patients (reviewed in (Pariante and Lightman, 2008), this system has also been shown to be dysfunctional in epilepsy: PWE (temporal and extratemporal foci) without comorbid depression or anxiety had greater elevation in cortisol following the dexamethasone/corticotrophin-releasing hormone (Dex/CRH) test compared to controls, indicative of a hyperreactive HPA axis (Zobel *et al.*, 2004). This is consistent with rat models of epilepsy (Mazarati *et al.*, 2009). Elevations in cortisol and adrenocorticotrophic hormone (ACTH) have also been reported after seizures (Gallagher *et al.*, 1984; Pritchard *et al.*, 1985; Takeshita *et al.*, 1986; Gallagher, 1987; Rao *et al.*, 1989; Kumar *et al.*, 2011). Animal studies provide insight on the cause/effect relationship between HPA axis dysfunction and epilepsy. Corticosterone supplementation enhances epileptogenesis in the amygdala kindling model (Karst *et al.*, 1999; Taher *et al.*, 2005; Kumar *et al.*, 2007), and conversely, retarded kindling rates have been demonstrated in surgically adrenalectomized rats compared with sham rats (Cottrell *et al.*, 1984; Weiss *et al.*, 1993; Edwards *et al.*, 1999). Additionally, early life stress, which is recognized to up-regulate HPA axis responsivity, imparts an enduring vulnerability to experimental limbic epileptogenesis (reviewed in Koe *et al.*, 2009). Together, this evidence suggests a faulty regulation of the HPA axis in epilepsy, and implicates a modulatory role for this system in epilepsy pathophysiology.

As mentioned above, increases in glucocorticoids are observed in ~50% of depressed patients (Holsboer, 2001), presumed to be due to dysfunctional negative feedback of the HPA axis. Interestingly, successful treatment in depressed patients with antidepressants, particularly SSRIs, can improve this impaired HPA axis regulation (Pariante, 2006; Himmerich *et al.*, 2007). Animal studies also demonstrate suppression of HPA axis function following antidepressant treatment (Jensen *et al.*, 1999; Jongsma *et al.*, 2005), an effect that may be due to observed increases in glucocorticoid and mineralocorticoid receptors (Pepin *et al.*, 1989; Reul *et al.*, 1993; 1994; Barden, 1999).

The ability of antidepressants to influence HPA axis regulation and the evidence suggestive of a detrimental role of glucocorticoids in epilepsy development promotes the HPA axis as a potential site of interaction whereby antidepressants could influence epileptogenesis and seizure susceptibility. Although a large number of studies have investigated HPA axis changes in epilepsy, and following antidepressant treatment individually, to date no studies have investigated neuroendocrine function in epilepsy specifically during antidepressant exposure.

Monoamines and other neurotransmitters

A broad literature describes monoamine abnormalities in the pathophysiology of both depression and epilepsy. Notably, PET studies in PWE show reduced hippocampal $5HT_{1A}$ receptor binding, reduced further with comorbid depression (Hasler *et al.*, 2007) and an inverse correlation between $5HT_{1A}$ receptor binding and severity of depressive symptoms (Theodore *et al.*, 2007). Since many of the new generation antidepressants target monoaminergic neurotransmission, these systems present prime candidates to mediate the influence of antidepressants on seizures and epilepsy development. As described above, the pharmacological target of SSRIs and SNRIs are the serotonin and/or noradrenaline transporters, and inhibition of these targets increases synaptic levels of these neurotransmitters. It appears unlikely that this is the sole mechanism of antidepressant activity since these drugs usually need to be taken for several weeks to become clinically effective. However, the acute increases in synaptic neurotransmitter levels may set in train downstream mechanisms critical to the actions of these drugs, so it is important to consider these acute effects as potentially relevant to any chronically observed effects. A broad range of studies has demonstrated that increases in monoamines induce antiepileptic effects in seizure models (for reviews, see (Bagdy *et al.*, 2007; Lu and Gean, 1998).

In addition to acute effects on seizure susceptibility, antidepressants could also affect epilepsy disease processes through monoaminergic mechanisms. In animals, lesioning noradrenergic inputs from the locus coeruleus accelerated amygdala kindling, implying an antiepileptogenic role for noradrenaline. Furthermore, the GEPR-9 rats display seizure susceptibility concurrent with noradrenergic deficits (Dailey and Jobe, 1986). Reversing these neurotransmitter deficits reduces the seizure susceptibility (Yan *et al.*, 1993), implying a causal relationship. Other studies have investigated the effects on serotonergic (Wada *et al.*, 1997) or noradrenergic agonists and antagonists (Shin and McIntyre, 2007) on seizures and epileptogenesis. For example, Wada *et al.* (1997) investigated disease progression using the kindling model following administration of serotonin receptor agonists and found that a $5HT_{1A}$ receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) inhibited kindling rate while a $5HT_2$ receptor agonist, 2,5-dimethoxy-4-iodoamphetamine (DOI) facilitated kindling (Wada *et al.*, 1997). The effect of DOI was blocked by the addition of a $5HT_2$ receptor antagonist, ketanserin. Activation of $5HT_{1A}$ receptors may also be relevant to acute effects of SSRIs on seizures: $5HT_{1A}$ receptor knockout mice demonstrate reduced seizure threshold (Sarnyai *et al.*, 2000) and increased mortality resulting from a seizure (Parsons *et al.*, 2001). Similarly, $5HT_{1A}$ receptor

antagonists have been shown to increase seizure severity and duration (Watanabe *et al.*, 2000; Pericic *et al.*, 2005), while agonists are protective against induced seizures (Hagan *et al.*, 1995; Gariboldi *et al.*, 1996). Moreover, activation of post-synaptic $5HT_{1A}$ receptors elicits powerful inhibitory effects on hippocampal electrophysiology (e.g. Blier and de Montigny, 1987). These studies suggest that $5HT_{1A}$ receptors may also be potential mediators of SSRI effects on seizures.

Preclinical studies have directly examined the influence of the serotonergic system in the effects of fluoxetine in epilepsy. Again, using the GEPRs, fluoxetine reduced the severity of sound-induced convulsions, and the time course of this effect paralleled the concurrent fluoxetine-induced rise in extracellular serotonin (Dailey *et al.*, 1992). Also, using the pilocarpine-induced post-status epilepticus model of epilepsy, chronic fluoxetine treatment reduced brain excitability and also restored the epilepsy-induced serotonergic deficits (Mazarati *et al.*, 2008). Intriguingly, the depression-like behavioural deficits associate with the model were *not* ameliorated by fluoxetine treatment, suggesting that depression in epilepsy may have distinct underlying mechanisms not related to serotonergic dysfunction. These initial results of preclinical studies provide promising support for a role of monoamines in mediating the effects of antidepressant on seizures and epileptogenesis.

Other neurotransmitter systems, including GABA and glutamate, may also be potential substrates of interaction for antidepressants on epileptogenesis. Imbalances in glutamate and GABA have long been implicated as the cause of convulsive seizures (Olsen *et al.*, 1999), being an important area of investigation for the management of seizures and potentially epileptogenesis. Some reports suggest that antidepressants can influence the GABAergic system (Krystal *et al.*, 2002), and while this suggests a future area of research, to date this evidence appears sparse. Similarly, effects of SSRIs on sodium (Pancrazio *et al.*, 1998; Wang *et al.*, 2008; Igelstrom and Heyward, 2012), potassium (Choi *et al.*, 1999, 2001; Yeung *et al.*, 1999; Lee and Kim, 2010; Lee *et al.*, 2010) and calcium (Deak *et al.*, 2000; Traboulsie *et al.*, 2006) channels have been reported, which may be a mechanism by which SSRIs exert an anticonvulsant effect. However, there have been few studies to investigate this but suggest that this also represent areas for future investigations.

Brain-derived neurotrophic factor (BDNF)

BDNF is a key regulator of neuronal plasticity in both health and disease. It has been heavily implicated in epilepsy development, not least because of its modulatory roles on excitatory and inhibitory neurotransmission (Elmariah *et al.*, 2004). BDNF is elevated in hippocampal tissue in PWE (Mathern *et al.*, 1997; Takahashi *et al.*, 1999; Murray *et al.*, 2000), and its synthesis is increased by acute seizures (Ernfors *et al.*, 1991; Rudge *et al.*, 1998).

Several studies have demonstrated pro-epileptogenic effects of BDNF, including observations of spontaneous seizures after intra-hippocampal infusion (Scharfman *et al.*, 2002) or transgenic overexpression of BDNF (Croll *et al.*, 1999). Also, genetic deletion of TrkB, the primary signalling target of BDNF, prevents kindling epileptogenesis (He *et al.*, 2004). Furthermore, BDNF elicits hyper-excitability in dentate granule cells in rodent (Asztely *et al.*, 2000; Koyama *et al.*, 2004) and human brain slices (Zhu and Roper, 2001). Conversely, others have demonstrated antiepileptic effects: chronic infusion of BDNF delays the development of electrical kindling (Larmet *et al.*, 1995; Osehobo *et al.*, 1999; Reibel *et al.*, 2000a; 2000b), effects that may be due to desensitization of the signalling pathway (Reibel *et al.*, 2000a), or to effects on neuropeptide Y and GABAergic inhibition (Koyama and Ikegaya, 2005).

BDNF has also been implicated in the aetiology of depression (Castren *et al.*, 2007) and many studies suggest that BDNF and its receptor TrkB are involved in the mechanisms of antidepressant action (D'Sa and Duman, 2002; Nestler *et al.*, 2002; Popoli *et al.*, 2002). Several clinical studies have reported increases in serum BDNF levels following antidepressant treatment in depressed patients, which correlates with improvements in mood (Karege *et al.*, 2002; Aydemir *et al.*, 2005; 2006; Gervasoni *et al.*, 2005; Gonul *et al.*, 2005). In animal models, increases in BDNF mRNA (Nibuya *et al.*, 1995; Russo-Neustadt *et al.*, 2000; Dias *et al.*, 2003) and protein (Chen *et al.*, 2001; Altar *et al.*, 2003; Xu *et al.*, 2003), as well as TrkB expression (Nibuya *et al.*, 1995) and activation (Saarelainen *et al.*, 2003) in the hippocampus and prefrontal cortex have been shown following antidepressant treatment; however, others have failed to demonstrate such elevations (Miro *et al.*, 2002; Coppell *et al.*, 2003; Altieri *et al.*, 2004). Functionally, these antidepressant-driven increases in BDNF and TrkB signalling may be essential for therapeutic activity (Duman *et al.*, 1997; Castren *et al.*, 2007; Adachi *et al.*, 2008; Li *et al.*, 2008). Despite the clear rationale for BDNF as an intermediary, to our knowledge, no studies have examined the role of neurotrophin signalling in antidepressant actions in seizures or epilepsy.

Inflammation

Inflammation is another biological process implicated in the pathogenesis of epilepsy (Vezzani *et al.*, 2012), which is also influenced by antidepressants (Janssen *et al.*, 2010). With respect to epilepsy, increases in inflammatory mediators have been identified in resected brain tissue from patients with temporal lobe epilepsy (Crespel *et al.*, 2002; Zattoni *et al.*, 2011; Hirvonen *et al.*, 2012) and in experimental seizure models (Minami *et al.*, 1991; Vezzani *et al.*, 2000; Turrin and Rivest, 2004; Gorter *et al.*, 2006). In some cases, such as following status epilepticus, these elevations can persist for weeks (Foresti *et al.*, 2009; Xu *et al.*, 2009). Moreover, various inflammatory mediators are involved in generating and exacerbating seizures (summarized in Vezzani *et al.*, 2011). For example, genetic and pharmacological blockade of Toll-like receptor-4 (Maroso *et al.*, 2010) or IL-1β (Vezzani *et al.*, 2000; Dube *et al.*, 2005) induces antiepileptic effects in animal models. Furthermore, patients with autoimmune disorders such as vasculitis or Crohn's disease may exhibit recurrent seizures (Najjar *et al.*, 2008), and animal models of infection exhibit increased seizure susceptibility (Sayyah *et al.*, 2003; Galic *et al.*, 2008; 2009; Auvin *et al.*, 2009), which may be due to the associated inflammation. Together this collective evidence promotes a causal role for inflammatory mechanisms in epileptogenesis and seizures.

Increases in various inflammatory mediators have also been reported in cases of depression. Most frequently reported is elevation of the cytokine, IL-6 (Maes *et al.*, 1995;

Tiemeier *et al.*, 2003; Alesci *et al.*, 2005; Brietzke *et al.*, 2009) with similar reports for IL-1β and TNF-α (Lanquillon *et al.*, 2000; Mikova *et al.*, 2001; Owen *et al.*, 2001). Treatment with SSRIs and SNRIs have anti-inflammatory effects, decreasing production of pro-inflammatory cytokines IL-1β, TNF-α, IFN-γ and increasing anti-inflammatory cytokines such as IL-10 (Kenis and Maes, 2002; Sutcigil *et al.*, 2007), although other studies have failed to replicate this (Hannestad *et al.*, 2011), or demonstrated pro-inflammatory effects of antidepressants (Piletz *et al.*, 2009; Fornaro *et al.*, 2011). Similar anti-inflammatory effects have been observed in animal studies where antidepressants attenuate cytokine production and concurrently reduce depressive-like symptoms (Castanon *et al.*, 2001; Yirmiya *et al.*, 2001; Song *et al.*, 2009).

These data postulate a role for inflammation in epilepsy, which could be modulated by concurrent antidepressant treatment. This is further supported by demonstration of an interaction between fluoxetine and IL-1β in the pilocarpine-induced post-status epilepticus model. In a series of studies, Mazarati and colleagues first showed that this model induces depressive-like behaviours, dysregulation of the HPA axis and abnormal serotonin signalling. They then demonstrated that two weeks of intrahippocampal infusion of IL-1 receptor antagonist (IL-1ra) improved the depression-like phenotype in these animals (but had no effect on spontaneous seizures) (Mazarati *et al.*, 2010). A subsequent study investigated the combination of fluoxetine and IL-1ra treatment in the same model, and found that while fluoxetine treatment in isolation had no effect, the combination treatment improved the depression-like behaviours and abnormalities in serotonin signalling, but only partially improving HPA axis hyper-reactivity (Pineda *et al.*, 2012). This indicates that co-treatment of antidepressants with IL-1 receptor blockers, or other anti-inflammatory agents, may be an effective therapy for treatment-resistant depression and may reverse some of the pathological processes associated with epilepsy development.

Conclusions

With psychiatric disorders contributing a large proportion of the comorbidity in epilepsy, management of these disorders has become of great importance. In this paper, we have highlighted some of the potential implications for treating these disorders with antidepressants in PWE, particularly the effects of these drugs on seizure susceptibility and on the potential interaction with processes that are associated with epilepsy development and progression. While much of the literature to date has focused on the effects of antidepressants on short term end points, such as effects on seizure thresholds, future studies should focus upon the effects of antidepressants on longer term end points, such as seizure frequency over time, and on the neurobiological alterations that may influence epileptogenesis. In this paper, several lines of indirect evidence regarding some common potential substrates of interaction have been highlighted, areas that may be considered in future investigations of the effects of antidepressants in epilepsy. Primary among these are investigations on the production and functioning of newborn granule cells, in particular how newborn cells are affected by antidepressant treatment in epilepsy, as well as assessment of serotonergic receptor alterations (function/expression), particularly the $5HT_{1A}$ receptor. Further exploration of the effects of antidepressants on ion channels and the influence of this on seizures and epilepsy are also warranted, given the emerging evidence in the area. Drugs targeting the serotonergic system, including SSRIs, should also be explored as potential therapies in treating epilepsy itself.

Overall, the majority of clinical and experimental data suggest that the effects of antidepressants on epilepsy itself are beneficial, indicating that antidepressants, in particular the newer generation compounds, SSRIs and SNRIs, should be considered safe for use in epilepsy. However, it is wise to be cautious of such data. While many studies have investigated how SSRIs affect seizures, few have investigated the underlying processes that may lead to the effects of SSRIs on seizures and in particular epileptogenesis. Future studies will need to investigate the effects of chronic SSRI exposure, investigating the effects on seizures at clinically relevant time points including prior to seizure onset, at onset and at the chronic stages, as well as investigating the effects on mediators of epileptogenesis and how these are altered with antidepressant treatment.

Conflict of interest

The authors have no conflicts of interest, financial or otherwise, associated with this work to disclose.

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