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Selective blockade of NK2 or NK3 receptors produces anxiolytic- and antidepressant-like effects in gerbils

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Abstract

There is a growing interest in the potential anxiolytic- and antidepressant-like effects of compounds that target neurokinin receptors. Since the structure and the pharmacology of the human neurokinin receptor resembles that of gerbils, rather than that of mice or rats, we decided to investigate the anxiolytic- and /or antidepressant-like effects of NK1 (SSR240600), NK2 (saredutant) and NK3 (osanetant) receptor antagonists in gerbils. It was found that saredutant (3–10 mg/kg, p.o.) and osanetant (3–10 mg/kg, p.o.) produced anxiolytic-like effects in the gerbil social interaction test. These effects were similar to those obtained with the V1b receptor antagonist SSR149415 (3–10 mg/kg, p.o.), diazepam (1 mg/kg, p.o.) and buspirone (10 mg/kg, p.o.). Fluoxetine and SSR240600 were devoid of effects in this test. In the tonic immobility test in gerbils, saredutant (5–10 mg/kg, i.p.) and osanetant (5–10 mg/kg, i.p.) produced similar effects to those observed with fluoxetine (7.5–15 mg/kg, i.p.), SSR149415 (10–30 mg/kg, p.o.) and buspirone (3 mg/kg, i.p.). Diazepam and SSR240600 were inactive in this paradigm. In conclusion, the present study indicates further that NK2 and NK3 receptor antagonists may have therapeutic potential in the clinical management of anxiety and depression.

Keywords: Neurokinin receptor; Anxiety; Depression; Social interaction; Tonic immobility; Gerbils; Osanetant; Saredutant

1. Introduction

Current treatments of depression and anxiety disorders may result in many adverse events (Maubach et al., 1999) and a substantial proportion of patients do not show adequate improvement with such treatments (Maubach et al., 1999). Novel strategies for pharmacological intervention include the use of drugs that interact with brain neuropeptide systems (Griebel, 1999; Holmes et al., 2003). Of these neuropeptides, substance P has been extensively studied and appears involved in the neuropathology of stress-related disorders (Bondy et al., 2003; Rimon et al., 1984). Substance P, neurokinin A and neurokinin B are part of the tachykinin family described in a variety of species (Khawaja and Rogers, 1996; Pennefather et al., 2004). They interact with specific G protein-coupled receptors; three subtypes have been identified (i.e. NK1, NK2, and NK3) (Regoli et al., 1994). Behavioural studies in rodents have shown that NK1 receptor antagonists possess anxiolytic and/or antidepressant properties (File, 1997, 2000; Gentsch et al., 2002; Kramer et al., 1998; Papp et al., 2000; Varty et al., 2002, 2003; Vassout et al., 1994, 2000; Steinberg et al., 2002). The selective NK2 receptor antagonists, GR159897 and SR48968 (saredutant), were effective in several animal models of anxiety (De Lima et al., 1995; Griebel et al., 2001; Stratton et al., 1993, 1994; Teixeira et al., 1996; Walsch et al., 1995). In addition to its anxiolytic-like activity, saredutant displayed antidepressant-like effects in the forced swim test in rats (Steinberg et al., 2001; Dableh et al., 2005). The effects of drugs acting at NK3 receptors on levels of anxiety and depression have been less investigated. Ribeiro et al. (1999) reported that the NK3 receptor agonist, senktide, decreased the level of anxiety of mice in the elevated-plus maze. Dableh et al. (2005) showed that the NK3 receptor antagonist, SR142801 (osanetant), displayed antidepressant-like effects in the rat forced swim test.

Species-related variations exist in the primary sequence of the NK1 receptor and these variations may affect the potency and efficacy of non-peptide antagonists in different species

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(Beresford et al., 1991; Saria, 1999; Varty et al., 2002). In particular, it has been suggested that gerbils would be a more suitable species than rats or mice for investigating the anxiolytic- and antidepressant-like effects of NK1 antagonists (Varty et al., 2002). Although less information is available concerning the NK2 and NK3 receptors, the NK3 receptor antagonist, osanetant, has higher affinity for the human and the gerbil than for the rat NK3 receptor (Emonds-Alt et al., 1995). Accordingly, the present study was undertaken to investigate further the actions of selective NK1 (SSR 240600) (Emonds-Alt et al., 2002), NK2 (saredutant) (Emonds-Alt et al., 1992) and NK3 (osanetant) (Emonds-Alt et al., 1995) antagonists in gerbil models of anxiety and depression, i.e. the social interaction (File et al., 2001) and the tonic immobility (Simiand et al., 2003) paradigms, respectively. For comparison, we examined the effects of several compounds with anxiolytic and/or antidepressant-like effects in rodents: buspirone, diazepam, fluoxetine and SSR149415, a selective V1b receptor antagonist (Griebel et al., 2002). Some of this work has been presented previously in abstract form (Salomé et al., 2004; Simiand et al., 2003).

2. Methods

2.1. Animals

Male Mongolian gerbils (*Meriones unguiculatus*, Janvier, Le Genest St-Isle, France), 7 weeks old (50–60 g), were used. Upon arrival, they were housed in groups of four (30×40×20 cm) in the animal facility room and maintained under a 12:12 LD cycle (lights on at 7:00) with ad libitum access to food and water. Behavioural tests were performed between 9:00 and 15:00. All procedures have been approved by the Comité d'Expérimentation Animale of Sanofi-Synthélabo Recherche and were carried out in accordance with the French legislation (decree 87-848, October 19, 1987; and order from April 19, 1988), which implemented the European directive 86/609/EEC.

2.2. Procedures

2.2.1. Social interaction test in gerbils

The procedure is that described by File et al. (2001). Testing lasted 2 days: a first habituation session on day 1 followed 24 h later by the test. For the habituation session, gerbils were placed individually in a plastic box (30×30×20 cm) under bright light (300 lux) for a 10-min free-exploration period. The following day, all gerbils were injected per os (p.o.) with vehicle or one dose of the test compound 60 min before testing was carried out. Thereafter, two gerbils from the same weight and the same treatment group but different cages were placed together in the experimental cage for a 4′30-min observation period. Interaction time was recorded manually and consisted in active behaviours such as grooming, chasing and playing. Five to ten couples of gerbils were tested per treatment group.

2.2.2. Tonic immobility in gerbils

The test is based on that described by Simiand et al. (2003). To induce tonic immobility, gerbils were held on a flat surface and were firmly pinched for 15 s at the scruff of the neck, using the thumb and the index finger. They were then gently placed on parallel bars (4 mm in diameter, spaced 5 cm apart and having a 3 cm difference in height; the lower bar was elevated 40 cm above the base). Tonic immobility was measured during 5 successive trials with 30 s inter-trial interval. A trial ended either when the animal started to move or after 90 s has elapsed. The total time of tonic immobility was calculated. Six to ten gerbils were tested per treatment group.

2.2.3. Locomotor activity in gerbils

Gerbils were placed in photocell activity cages (43×28×20 cm high, Imetronic, Pessac, France) equipped with two horizontal photobeam arrays 2 cm above the floor. The number of beam breaks was recorded automatically during 10 min by computer using the Imetronic software. Eight to eleven gerbils were tested per treatment group.

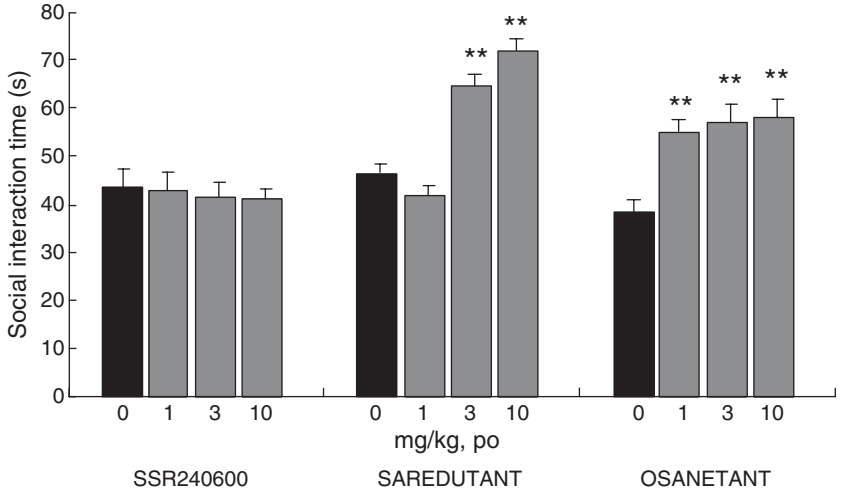

Fig. 1. Effects of SSR240600, saredutant and osanetant on the duration of social interaction in gerbils. Data represent means±SEM. **$p<0.01$ as compared to the vehicle-treated control group.

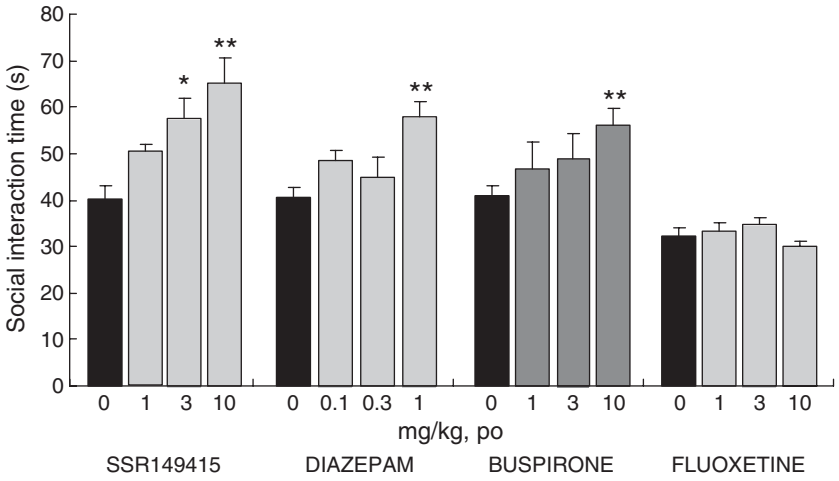

Fig. 2. Effects of SSR149415, buspirone, fluoxetine and diazepam on the duration of social interaction in gerbils. Data represent means ± SEM. *$p<0.05$, **$p<0.01$ as compared to the vehicle-treated control group.

2.3. Drugs

SSR240600, [(R),-2-(1-{2-[4-{2-[3,5-bis(trifluoromethyl) phenyl]acetyl}-2-(3,4-dichlorophenyl)-2-morpholinyl]ethyl}-4-piperidinyl)-2methylpropanamide]; SR48968 (saredutant), ((*S*)-*N*-methyl-*N*-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl) butyl] benzamide); SR142801 (osanetant), *N*-[1-[3[1-benzoyl-3-(3, 4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-4-piperidinyl]-*N*-methyl-, monohydrochloride; SSR149415 ((2S, 4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl) sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidinecarboxamide) were synthesised by the CNS Medicinal Chemistry Department of Sanofi-Synthelabo Recherche (Montpellier, France). Buspirone and fluoxetine were purchased from Sigma Aldrich (St Quentin Fallavier, France). Diazepam was obtained from Roche (Basel, Switzerland). SSR240600, saredutant, osanetant, diazepam and fluoxetine were dissolved in physiological saline containing 0.1% Tween 80 (Sigma). SSR149415 was dissolved in physiological saline with 5% DMSO/Cremophor (Sigma). Control groups received the appropriate vehicle.

In the social interaction test, all drugs were administered per os (p.o., 20 ml/kg) 60 min before testing was carried out. In the tonic immobility test and locomotor activity test, all drugs were given intraperitoneally (i.p., 20 ml/kg) 30 min before testing except for SSR149415 (p.o., 60 min). Doses were selected based on previous results on animal models of affective disorders (Jung et al., 1996; Griebel et al., 2001, 2002; Steinberg et al., 2002).

2.4. Statistics

Data were analysed by one-way ANOVA followed by Dunnett's test or, when variances were not equal, with the non-

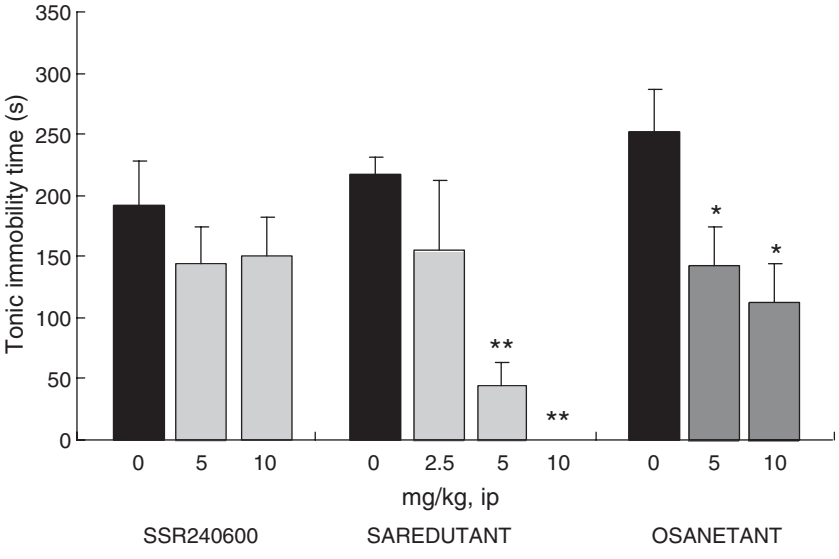

Fig. 3. Effects of SSR240600, osanetant and saredutant on the duration of tonic immobility in gerbils. Data represent means ± SEM. *$p<0.05$, **$p<0.01$ as compared to the vehicle-treated control group.

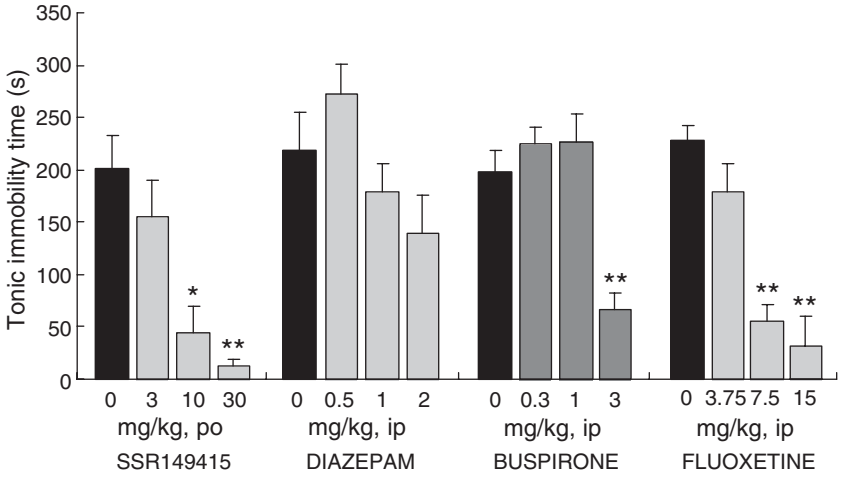

Fig. 4. Effects of SSR149415, diazepam, buspirone and fluoxetine on the duration of tonic immobility in gerbils. Data represent means±SEM. *$p<0.05$, **$p<0.01$ as compared to the vehicle-treated control group.

parametric Kruskall–Wallis test followed by Mann Whitney *U*-test.

3. Results

3.1. Social interaction test

As shown in Fig. 1, saredutant (3 and 10 mg/kg) and osanetant (1, 3 and 10 mg/kg), but not SSR240600, significantly increased social interaction time [F (3,19)=13.33, $p<0.001$; F (3,18)=6.98, $p<0.01$; F (3,23)=0.16 n.s.; respectively]. An increase of social interaction was also observed after administration of SSR149415 (3 and 10 mg/kg), diazepam (1 mg/kg) and buspirone (10 mg/kg) [F (3,19)=5.81, $p<0.01$; F (3,19)=3.65, $p<0.05$; F (3,39)=4.3, $p<0.05$, respectively] but not after treatment with fluoxetine [F (3,55)=1.67, n.s.] (Fig. 2).

Table 1
Effects of SSR2404600, saredutant, osanetant, SSR149415, diazepam, buspirone and fluoxetine on the number of beam break interruptions recorded during the locomotion test

Compound (mg/kg)	Number of beam breaks mean±SEM	Compound (mg/kg)	Number of beam breaks mean±SEM
SSR240600		Diazepam	
0	90.2±15.8	0	95.9±16.6
5	65.1±11.2	0.5	98.8±21.2
10	72.1±14.7	1	57.2±12.8
		2	114.7±57.5
Saredutant		Buspirone	
0	59.4±16.5	0	116.5±23.9
2.5	49.8±11.5	0.3	80.9±16.4
5	33.5±6.5	1	69.9±14.1
10	24±6.3	3	75.8±7.9
Osanetant		Fluoxetine	
0	86.3±9.8	0	80.4±18.3
5	100.1±14.7	3.75	87.2±17.6
10	65.4±19	7.5	71.1±8.4
		15	112.9±33.5
SSR149415			
0	36.3±10.7		
3	65.8±20.9		
10	65.8±13.1		
30	38.9±16		

Data represent means±SEM.

3.2. Tonic immobility test

As shown in Fig. 3, saredutant (5 and 10 mg/kg) and osanetant (5 and 10 mg/kg), but not SSR240600 decreased immobility time [$H=21.63$, $df=3$, $p<0.0001$; F (2,29)=5.04, $p<0.05$]. SSR149415 (10 and 30 mg/kg), buspirone (3 mg/kg) and fluoxetine (7.5 and 15 mg/kg) also decreased immobility [$H=16.18$, $p<0.005$; F (3,30)=14.04, $p<0.05$; F (3,30)=21.58, $p<0.05$, respectively], whereas diazepam did not produce any significant effect [F (2,35)=2.77, n.s.] (Fig. 4).

3.3. Locomotor activity

None of the drugs modified significantly spontaneous locomotor activity when tested at the doses used in the social interaction and tonic immobility tests (Table 1) [saredutant, F (3,31)=2.03; osanetant, F (2,29)=1.35; SSR240600, F (2,32)=0.88; SSR149415, F (3,40)=1.09; buspirone, F (3,36)=1.60; diazepam, F (3,36)=0.57 and fluoxetine, F (3,32)=0.70].

4. Discussion

The present study shows that acute administration of saredutant, a selective NK2 receptor antagonist, and osanetant, a selective NK3 receptor antagonist, produce anxiolytic- and antidepressant-like effects in gerbils as assessed by the social interaction and the tonic immobility paradigms, respectively. In contrast, SSR240600, a selective NK1 receptor antagonist, did not affect emotional responses in these tests.

The social interaction test, classically used in rats (File and Seth, 2003), has been recently adapted in gerbils by File et al. (2001). In the present study, saredutant, osanetant, SSR149415, diazepam and buspirone increased the amount of social interaction, whereas SSR240600 and fluoxetine were without effect.

The profile of action of saredutant and osanetant was similar to that observed with SSR149415, a V1b receptor antagonist, which displays anxiolytic-like effects in classical (punished drinking and elevated plus-maze) and atypical (fear/anxiety defense test battery, social defeat-induced anxiety) rodent models of anxiety (Griebel et al., 2002, 2003). This is the first study to show an anxiolytic-like effect with a NK2 antagonist in gerbils. The anxiolytic-like profile of saredutant in the present study is in agreement with results from previous studies. In exploration-based procedures, such as the elevated plus-maze and the light/dark tests in rats or mice, NK2 receptor antagonists (GR1000679, GR159897, saredutant) produced anxiolytic-like effects (Griebel et al., 2001; Stratton et al., 1993, 1994; Teixeira et al., 1996). Anxiolytic-like properties of saredutant have also been reported in the mouse defence test battery (Griebel et al., 2001) and in the marmoset human intruder test (Walsch et al., 1995). This is the first study to investigate the effects of an NK3 receptor antagonist in an anxiety test in gerbils. The anxiolytic-like effects of osanetant observed in the present study contrast with those produced by senktide, an NK3 receptor agonist, in the elevated plus-maze in mice following intracerebroventricular injection (Ribeiro and De Lima, 1998; Ribeiro et al., 1999). In particular, intracerebral injection of senktide induced anxiolytic-like effects in the elevated plus-maze in mice which was blocked by administration of the NK3 antagonists [Trp7β-Ala8]NKA (4–10) and osanetant (Ribeiro et al., 1999; Ribeiro and De Lima, 2002). The reason for this difference is unclear, but may be due at least partially to species differences. In rats and mice, NK1 receptor antagonists produced anxiolytic-like effects (Teixeira et al., 1996; Santarelli et al., 2001; Varty et al., 2002; File, 1997, 2000; Vassout et al., 1994, 2000), although negative results have also been reported (Nikolaus et al., 1999; Rodgers et al., 2004; Loiseau et al., 2003) probably due to strain-, sex-, test-differences (Rodgers et al., 2004; Vendruscolo et al., 2003; McLean, 2005). In contrast to the lack of effect obtained in the present study, NK1 receptor antagonists have been shown to produce anxiolytic-like effects in gerbils in the elevated plus-maze and social interaction tests (Cheeta et al., 2001; Gentsch et al., 2002, Varty et al., 2002). SSR240600 has been shown to antagonize various NK1 receptor-mediated pharmacology effects in the periphery and in the central nervous system (Emonds-Alt et al., 2002; Steinberg et al., 2002). The reason of a lack of effect of SSR240600 in the present study is therefore unknown.

To investigate further the profile of action of SSR240600, saredutant and osanetant in gerbils, tonic immobility test was performed. This test is based on the reduction of an innate defence response characterised by a temporary state of profound and reversible motor inhibition, the tonic immobility. This reaction is reduced by antidepressant in mice (Fundaro, 1998) and in gerbils (Simiand et al., 2003). In our study, saredutant, osanetant, fluoxetine, buspirone and SSR149415 decreased tonic immobility, whereas SSR240600 and diazepam failed to decrease this reaction. The antidepressant-like effects of saredutant in the gerbil tonic immobility test are in agreement with previous studies where a reduction of immobility in the forced swim test in mice and rats was observed (Dableh et al., 2005; Steinberg et al., 2001). This is the first study reporting antidepressant-like effects of osanetant in gerbils. Our result is in apparent contradiction with the antidepressant-like effect of the NK3 receptor agonist, aminosenktide in the forced swim test in mice (Panocka et al., 2001), suggesting that the sensitivity to NK3 receptor ligands may depend on the strains and species. Antidepressant-like effects of NK1 receptor antagonists have been found in the forced swim test in rats and mice (Rupniak et al., 2001; Dableh et al., 2005; Zocchi et al., 2003), in a chronic mild stress-induced decrease in sucrose consumption in rats (Papp et al., 2000) as well as in the tail suspension test performed in gerbils (Varty et al., 2003). However, the NK1 receptor antagonist, NKP608, failed to produce antidepressant-like effects in the tail-suspension or forced swim test (Rupniak et al., 2001; Bilkei-Gorzo et al., 2002; Brocco et al., 2002). The lack of effect of SSR240600 obtained in the present study both in the tonic immobility and the social interaction tests needs further investigation as it has been shown previously that SSR240600 has anti-stress effects (Steinberg et al., 2002). It suppressed distress vocalisations displayed by guinea pig pups after maternal separation (Steinberg et al., 2002), a model that was reported to be sensitive to antidepressant but also anxiolytic drugs (Kramer et al., 1998; Molewijk et al., 1996; Rupniak et al., 2000; Steinberg et al., 2001).

NK1 and NK3 receptors are widely distributed in the central nervous system in rodents and humans, the NK1 receptor being the predominant tachykinin receptor (Rigby et al., 2005). In contrast, expression of NK2 receptors is extremely limited in the adult central nervous system. They have been identified in the cortex, hippocampus, amygdala, thalamus and septum of rats and gerbils (Rigby et al., 2005) and in low levels in the human brain (Bensaid et al., 2001). Such a localization of tachykinin receptors, in particular in the cortex, amygdala, hippocampus and septum, is consistent with the anxiolytic- and antidepressant-like effects of saredutant and osanetant observed in the present study.

In conclusion, this study demonstrated that NK2 and NK3, but not NK1 receptor antagonists were able to reduce both anxiety- and depressive-related behaviours in gerbils. From a clinical point of view, it might be advantageous to have compounds with both an antidepressant and an anxiolytic action since many patients have mixed diagnoses.

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