Clinical Experience With Substance P Receptor (NK_1) Antagonists in Depression

K. Ranga R. Krishnan, M.B., Ch.B.

Substance P (SP) belongs to the neurokinin (NK) family of neuropeptides and exerts its biological effects via interaction with the NK_1 receptor. The SP-NK_1 receptor system is one of the best-characterized neurotransmitter pathways in both the central and peripheral nervous systems. It has been postulated that this pathway may have important roles in a variety of centrally regulated pathophysiologic conditions, including depression. In animal models, central injection of SP was associated with a series of anxiety-like behaviors, and this response could be abolished by pretreatment with SP (NK_1) receptor antagonists (SPAs). On the basis of these and other encouraging preclinical results, several clinical trials have examined the potential of SPAs in the treatment of depression. In phase 2 trials, therapy with the SPAs aprepitant (MK-0869) and compound A resulted in improvements in depression and anxiety symptoms that were quantitatively comparable with those seen with selective serotonin reuptake inhibitors (SSRIs) and significantly greater than those seen with placebo. These positive results have established a proof of concept that the inhibition of the SP-NK_1 receptor pathway may be a potentially useful novel treatment option for management of patients with depression. The apparent lack of benefit with SPAs versus placebo in subsequent dose-finding studies with aprepitant and compound A is not surprising, considering the fact that the outcomes with an active control (SSRI) in these trials were also similar to those observed with placebo. Future trials with SPAs will focus on the identification of appropriate patients and drug regimens and will also define the role of these agents in the treatment of depression.
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Depression is one of the most common disorders in the Western world. In the United States alone, depression is estimated to affect more than 18 million adults annually,[1] with approximately 2-fold higher prevalence in women than in men.[2] In addition, depression is also relatively frequent among adolescents, with high recurrence rates during adulthood.[3] Despite recent advances in pharmacologic therapy, a substantial proportion of patients with depression do not respond to currently available agents (or have only a partial response) and/or experience adverse effects. For these reasons, there is a need for antidepressant medications with a novel mechanism of action. Such therapies would be particularly useful if they provided higher response rates or if they had a more favorable tolerability/safety profile than currently available antidepressants.

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Corresponding author and reprints: K. Ranga R. Krishnan, M.B., Duke University Medical Center, Box 3950/4584, Clinical Research II, Durham, NC 27715 (e-mail: krish001@mc.duke.edu).

One of the most promising avenues in the search for novel antidepressant therapies is focused on the inhibition of the substance P (SP)–neurokinin-1 (NK_1) receptor pathway.[4] The rationale for targeting this pathway is based on several lines of evidence. First, the SP-NK_1 receptor system is one of the best-studied neurotransmitter pathways in the central nervous system (CNS), and numerous studies have demonstrated that the expression of SP and NK_1 receptors in the brain is localized to regions involved in the regulation of affective behavior (such as depression and anxiety) and stress response (e.g., amygdala, hypothalamus, hippocampus, frontal cortex, raphe nuclei, locus ceruleus), as reviewed by Saria.[5] Second, there is a considerable spatial (and therefore functional) overlap between the SP-NK_1 receptor system and other neurotransmitter (e.g., norepinephrine, serotonin) pathways with well-established roles in depression. Some CNS neurons co-express SP, norepinephrine, and serotonin, suggesting a possibility that the clinical manifestations of depression may be regulated by a complex network of interactions between these pathways.[6] Third, preclinical studies have shown that the central injection of an NK_1 receptor agonist results in anxiety-like behavioral effects.[7] Finally, a post-mortem analysis of cerebrospinal fluid revealed increased concentrations of SP among patients with depression,[8] although this finding could not be replicated in a later study.[9] Taken together, this evidence indicated that the

activity of the SP-NK_1 receptor system may play an important role in the etiology of depression and that the inhibition of this pathway may provide clinically meaningful antidepressant effects.

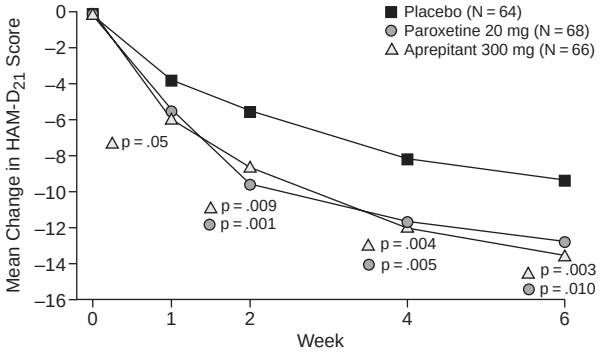
Initial studies with SP (NK_1) receptor antagonists (SPAs) sought to confirm their therapeutic potential in animal models of affective behavior. In early experiments with gerbils, several SPAs (aprepitant [MK-0869]; its analog L-760,735; and the structurally different agent L-733,060) were shown to strongly inhibit foot tapping (anxiety-like behavior) induced by central infusion of an NK_1 receptor agonist.[10] Additional studies in guinea pigs further showed that systemic pretreatment with the SPA L-733,060, the tricyclic imipramine, and the selective serotonin reuptake inhibitor (SSRI) fluoxetine, but not with the anxiolytics diazepam and buspirone, substantially attenuated audible, long-lasting vocalizations induced by central administration of an NK_1 receptor agonist.[6] This finding established that the anxiogenic effects produced by activation of NK_1 receptors in the brain can be abolished not only by SPAs, but also by currently available antidepressants, confirming the functional overlap between various neurotransmitter pathways and the potential clinical utility of an SPA for treatment of depression. Subsequent studies in guinea pigs further showed that the vocalizations induced by transient maternal separation (which mimic those induced by central infusion of an NK_1 receptor agonist) were markedly suppressed by subcutaneous or intraperitoneal treatment with antidepressants (phenelzine, imipramine, fluoxetine), anxiolytics (diazepam, buspirone), or high-affinity, brain-penetrating SPAs (L-760,735; L-733,060).[6] Moreover, similar effects were observed in response to orally administered SPAs L-760,735 and aprepitant, which indicated their suitability as oral therapeutic candidates for clinical trials.[6] In contrast, the SPAs with low affinity for NK_1 receptors and those with low CNS penetration showed only a weak ability to inhibit separation-induced vocalizations.[6] On the basis of these positive results in preclinical studies, clinical trials with orally bioavailable, brain-penetrating SPAs were initiated.

CLINICAL EXPERIENCE WITH SPAs IN PATIENTS WITH DEPRESSION

Aprepitant

Aprepitant is characterized by a high affinity and selectivity for the human NK_1 receptor, with no significant pharmacologic activity against receptors for other neurotransmitters implicated in depression (norepinephrine, serotonin, dopamine).[6] In addition to these factors, the choice of this agent for clinical studies was based on its high oral bioavailability, ability to penetrate the brain, and long duration of pharmacologic effect. The selection of the 300-mg once-daily dose of aprepitant for clinical evaluation was guided by its predicted ability to provide > 90% inhibition of the central NK_1 receptors (based on pharmacokinetic modeling) and by its good tolerability in an early study in healthy volunteers.[6]

Figure 1. Mean Change From Baseline to Week 6 in the Hamilton Rating Scale for Depression ($HAM\text{-}D_{21}$) Score in Patients With Major Depressive Disorder in the Phase 2 Trial With Aprepitant[a]

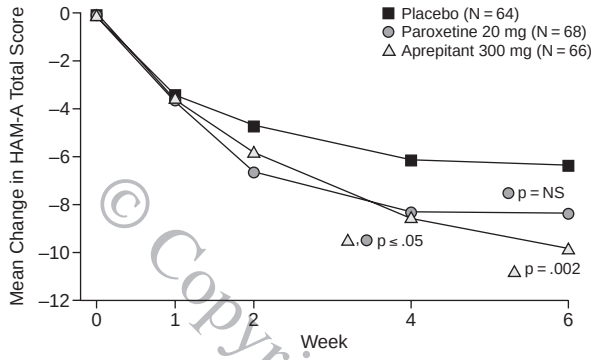


[a]Reprinted with permission from Kramer et al.[6] Comparisons are of aprepitant or paroxetine versus placebo.

Phase 2 trial. A 6-week, randomized, double-blind study in men and women with major depressive disorder and moderately high anxiety compared the tolerability/safety and efficacy of a single daily dose of aprepitant (300 mg) versus the SSRI paroxetine (20 mg once a day) and placebo.[6] Patients were eligible for enrollment if they had a DSM-IV diagnosis of major depressive disorder (single or recurrent), a current episode of depression lasting at least 4 weeks (but less than 2 years), a score ≥ 22 (moderately depressed) on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$), a score ≥ 15 (moderately high anxiety) on the Hamilton Rating Scale for Anxiety (HAM-A), and a score ≥ 4 (moderately ill) on the Clinical Global Impressions-Severity of Illness scale (CGI-S). Patients considered at risk for suicide or violence were excluded. Following a washout of previous psychotropic medications, a total of 213 outpatients were randomly assigned to receive aprepitant (N = 71), paroxetine (N = 72), or placebo (N = 70). Efficacy was monitored at the end of weeks 1, 2, 4, and 6 (or at the time of discontinuation). The primary efficacy outcome measure was the total score on the 21-item HAM-D, and secondary outcome measures included HAM-A total score and CGI-S score. Mean baseline $HAM\text{-}D_{17}$ score was approximately 25 in all 3 arms. The discontinuation rates in the 3 arms were similar (23% in the placebo arm, 36% in the paroxetine arm, and 28% in the aprepitant arm).

After 6 weeks of therapy, improvement in $HAM\text{-}D_{21}$ score with aprepitant was similar to that seen with paroxetine and significantly greater (by 4.3 points) than that observed with placebo (Figure 1).[6] The beneficial effects of aprepitant (and paroxetine) on $HAM\text{-}D_{21}$ scores first became evident after 1 week of treatment and continued to

Figure 2. Mean Change From Baseline to Week 6 in the Hamilton Rating Scale for Anxiety (HAM-A) Score in Patients With Major Depressive Disorder and Moderately High Anxiety in the Phase 2 Trial With Aprepitant[a]



[a]Reprinted with permission from Kramer et al.[6] Comparisons are of aprepitant or paroxetine versus placebo.

accrue during the entire course of therapy (see Figure 1). Furthermore, the proportion of patients who reached HAM-D_{17} scores < 10 (complete response) at the end of treatment in the aprepitant group was higher than in the paroxetine group and significantly higher than in the placebo group (43% vs. 33% vs. 17%, respectively; p = .001 for comparison of aprepitant vs. placebo; p = .026 for comparison of paroxetine vs. placebo).[6] In addition, the incidence of ≥ 50% reduction in HAM-D_{21} scores from baseline to week 6 was highest in the aprepitant arm (54% vs. 46% with paroxetine vs. 28% with placebo; p = .001 for comparison of aprepitant vs. placebo; p = .020 for comparison of paroxetine vs. placebo). These results provided a proof of concept that SPAs have significant clinical potential for treatment of depression.

In the phase 2 trial, aprepitant was also associated with significantly greater improvement in symptoms of anxiety. After 6 weeks of therapy, reduction in the total HAM-A score versus baseline in the aprepitant arm was 3.6 points higher than in the placebo arm (p = .002; Figure 2).[6] Similar to the effects on HAM-D_{21} scores, the improvement in anxiety symptoms with aprepitant continued to increase over time. On the other hand, the improvement in HAM-A score at 6 weeks with paroxetine was not significantly greater than that observed with placebo.[6] These results suggested that SPAs may also be useful anxiolytics.

Study drug treatment in this trial was discontinued because of adverse effects in 9% of patients in the placebo and aprepitant groups and in 19% of those treated with paroxetine (primarily nausea). The incidence of adverse events in patients treated with aprepitant was similar to that seen in patients receiving placebo (Table 1), suggesting acceptable tolerability and safety of this agent. Most of the adverse events in both the placebo and aprepitant arms were mild and transient. The rates of nausea, sexual dysfunction, anorexia, and sweating, which are typical side

Table 1. Incidence of Adverse Events (%) in the Phase 2 Trial With Aprepitant[a]

Adverse Event	Placebo (N = 70)	Paroxetine (N = 72)	Aprepitant (N = 71)
Headache	24	28	32
Somnolence	9	19	20
Nausea	10	29[b]	18
Asthenia/fatigue	4	19[b]	14
Diarrhea	9	15	11
Insomnia	9	14	11
Anorexia	3	11	4
Sweating	3	11	3
Sexual dysfunction	4	26[c]	3[d]

[a]Adapted with permission from Kramer et al.[6]
[b]p < .01 vs. placebo.
[c]p < .001 vs. placebo.
[d]p < .001 vs. paroxetine.

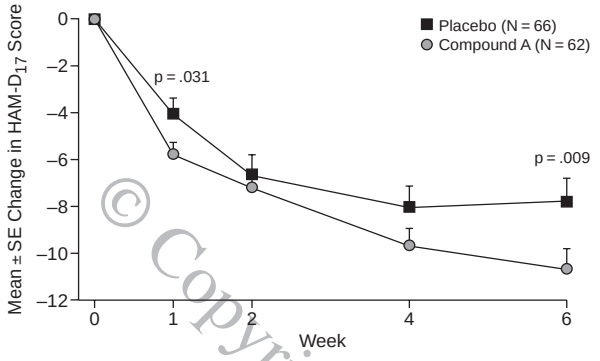
effects of SSRIs, were substantially higher in paroxetine-treated patients than in those receiving aprepitant or placebo (Table 1). Notably, sexual dysfunction was significantly more common among patients in the paroxetine group than in those receiving aprepitant (p < .001) or placebo (p < .001).[6]

Dose-finding study. Positive results of the phase 2 trial prompted a subsequent dose-finding study with aprepitant.[4] This 6-week, multicenter, parallel-group study (125 patients per group) evaluated the efficacy and tolerability/safety of 4 dosing regimens of aprepitant (10 mg, 30 mg, 100 mg, and 300 mg, once daily) versus the active (fluoxetine 20 mg, once daily) and placebo controls. The entry criteria and efficacy outcomes measured in this study were similar to those in the phase 2 trial. Approximately two thirds of the subjects were women, and the mean baseline HAM-D_{17} score was ≈25. The rate of discontinuation due to lack of efficacy or adverse effects was low and uniform, with a completion rate of approximately 75% in all treatment groups.

Improvements in HAM-D_{17} scores at 6 weeks were quantitatively similar in all treatment arms, including the fluoxetine arm and the various aprepitant arms.[4] In the absence of positive results with an active control (fluoxetine), no valid conclusions could be made regarding the clinical antidepressant efficacy of aprepitant. It is important to stress that the lack of effect with well-established antidepressants such as fluoxetine is not uncommon, as approximately 50% of all trials with various antidepressants have had similar, negative results.[4] Despite the overall negative findings in this study, there was a strong trend toward beneficial effects of both aprepitant (300-mg dose) and fluoxetine in more severely depressed patients (baseline HAM-D_{17} score ≥ 26), which indicated that SPAs (and SSRIs) may be particularly effective in those subjects.[11] This issue is likely to be addressed in future trials with SPAs and other novel antidepressants.

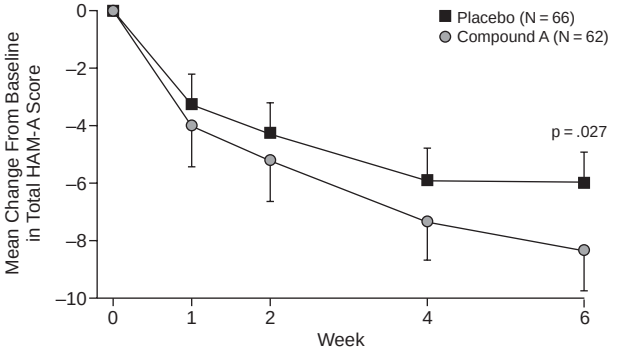
The tolerability and safety of aprepitant in the dose-finding study were similar to placebo. The rate of discontinuations due to adverse events was low and comparable

Figure 3. Mean ± SE Change From Baseline to Week 6 in the Hamilton Rating Scale for Depression (HAM-D_{17}) Score in Patients With Major Depressive Disorder in the Phase 2 Trial With Compound A[a]



[a]Data from Kramer.[11] Error bars indicate the standard error of the mean.

Figure 4. Mean Change From Baseline to Week 6 in the Hamilton Rating Scale for Anxiety (HAM-A) Score in Patients With Major Depressive Disorder and Moderately High Anxiety in the Phase 2 Trial With Compound A[a]



[a]Data from Kramer.[11] Error bars indicate the standard error of the mean.

across the various arms (range, 4%–7%). Importantly, none of the adverse events with aprepitant were dose related or occurred at a rate of > 10% (with 2-fold increase over placebo).[11]

Compound A

Following the completion of the dose-finding trial with aprepitant, a new SPA known as "compound A" became available for clinical evaluation.[11] Similar to aprepitant, compound A is characterized by high oral bioavailability and brain penetration, as well as by high selectivity and affinity for the NK_1 receptor.

Phase 2 trial. The efficacy and safety of compound A were initially investigated in a phase 2 trial in patients with a major depressive disorder.[11] Study design, entry criteria, and efficacy outcomes measured in this study were similar to those in earlier trials with aprepitant. Male and female outpatients were randomly assigned to receive either placebo (N = 66) or compound A (N = 62). Mean baseline HAM-D_{17} and HAM-A scores were ≈28 (higher than in studies with aprepitant) and ≈25, respectively. Approximately 70% of patients were women, and the average age of the study population was 40 years. A full 6-week course of therapy was completed by 65% of the patients.

Similar to the positive results with aprepitant in the phase 2 trial, compound A provided significantly greater improvement in HAM-D_{17} score at 6 weeks than placebo (Figure 3).[11] The magnitude of difference in HAM-D_{17} scores between the 2 arms increased continuously during the course of 6-week therapy, and the proportion of patients with ≥ 50% response at 6 weeks was considerably greater in the compound A arm (37% vs. 25% with placebo). Additionally, the reduction in the total HAM-A score at 6 weeks was significantly greater in patients receiving compound A ($p = .027$; Figure 4), reminiscent of the results obtained with aprepitant in the phase 2 study.[11] Considerable improvement in CGI-S scores (very much improved or much improved) at 6 weeks was reported by 47% of patients in the compound A group versus 21% of those treated with placebo ($p < .014$; odds ratio, 3.22), and the average improvement in CGI-S score at 6 weeks was also significantly greater in patients treated with compound A ($p = .009$).[11] These findings further confirmed therapeutic potential of SPAs for treatment of affective disorders, including depression.

The incidence of adverse events in the placebo and compound A groups was similar (Table 2), the only exception being a higher rate of somnolence in patients receiving compound A.[11] Notably, adverse effects frequently associated with currently available antidepressants (sexual dysfunction, weight gain, and gastrointestinal disturbances) occurred rarely in patients treated with compound A.

Dose-finding trial. In the dose-finding trial, outpatients with major depressive disorder were randomly assigned to receive 1 of 4 treatments (≈90 patients per group): placebo, paroxetine (20 mg), low-dose compound A, or high-dose (twice as high as low-dose) compound A.[11] Study drug was administered once daily for 8 weeks, and the trial was conducted at 10 centers. Entry criteria and efficacy outcomes assessed were similar to those in the phase 2 trial with compound A and studies with aprepitant. Mean baseline HAM-D_{17} and HAM-A scores were ≈25, the mean age of the study patients was 40 years, and approximately 75% of patients were women. The 8-week therapy was completed by ≈70% of the subjects, with no significant differences among various groups.

At 6 weeks, the improvements in mean HAM-D_{17} scores in various groups were comparable[11]; these results are qualitatively similar to those obtained in the dose-finding trial with aprepitant.[4] As discussed previously, the lack of benefit with the active control (paroxetine) precludes clinically meaningful inferences regarding the anti-

Table 2. Incidence of Adverse Events (%) in the Phase 2 Trial With Compound A[a]

Adverse Event	Placebo (N = 65)	Compound A (N = 62)
Any	65	76
Headache	15	17
Somnolence	2	17[b]
Nausea	7	14

[a]Data from Kramer.[11]
[b]$p < .05$ vs. placebo.

depressant activity of compound A in this trial. At the same time, it is important to reemphasize that about 50% of the clinical trials with different antidepressants were also negative, suggesting that this is a recurring issue in this therapeutic area.[4] One possible explanation for the negative results of the dose-finding trial with compound A is the inclusion of patients with less severe depression ($HAM\text{-}D_{17}$ score < 26), who may derive little or no benefit from established (e.g., SSRIs) or novel (SPAs) antidepressants. As shown in the dose-finding study with aprepitant, patients with more severe symptoms of depression ($HAM\text{-}D_{17}$ score ≥ 26) experience a substantial improvement in response to therapy with SPAs and SSRIs, whereas a smaller effect is observed in patients with less severe depression ($HAM\text{-}D_{17}$ score < 26).[11] Appropriate selection of patients who are most likely to benefit from SPAs and currently available antidepressants will, therefore, represent one of the key issues in future trials with these agents.

The percentage of patients who experienced any adverse event in this trial was similar across the 4 groups. Nausea and urogenital effects were substantially more common with paroxetine than with either placebo or compound A,[11] reminiscent of the results seen in the phase 2 trial with aprepitant.[6] Somnolence was more frequent among patients treated with compound A, although this effect was not dose related.

CONCLUSIONS AND FUTURE ISSUES

The $SP\text{-}NK_1$ receptor pathway in the CNS has been implicated in the pathophysiology of several centrally controlled disorders, including depression. For this reason, inhibition of this pathway has been suggested as a rational and novel approach to treatment of depression. Preclinical studies with various SPAs have confirmed their therapeutic potential, laying the foundation for clinical trials. Positive results of phase 2 trials with 2 different SPAs (aprepitant and compound A) validate the concept that these agents may be clinically useful antidepressants. Dose-finding trials with these agents showed that improvements in HAM-D and HAM-A scores with active controls (SSRIs) were similar to those seen with placebo (as previously seen in half of the trials with various antidepressants), allowing no conclusions about the therapeutic potential of SPAs in depression. It is important to note, however, that patients with more severe depression ($HAM\text{-}D_{17}$ score ≥ 26) in the dose-finding trial with aprepitant experienced considerable improvement in depression symptoms with this agent, as well as with an SSRI. Appropriate patient selection thus appears to be one of the most important issues that needs to be addressed in future trials with SPAs. Another important goal in these trials will be to definitively establish the correlation between the dose and clinical effect ("dose-response" relationship). Recent discovery of a radioactive, brain-penetrant nonpeptide tracer with high affinity for the NK_1 receptor, which permits real-time imaging of occupancy of this receptor in living human subjects via positron emission tomography imaging, may be particularly useful in this respect. Use of this tracer will permit quantification of NK_1 receptor occupancy with various doses of SPAs and define the degree and duration of receptor occupancy required to achieve consistent antidepressant effects, allowing dose optimization. Furthermore, this tracer may also be used to monitor NK_1 receptor occupancy in response to currently available therapeutic agents and to compare the $SP\text{-}NK_1$ pathway activity in patients with depression versus control subjects. Collectively, these studies will improve our understanding of the pathophysiology of depression and define the role of SPAs in the treatment of this disorder.

Drug names: buspirone (BuSpar and others), diazepam (Valium and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil), phenelzine (Nardil).

REFERENCES

1. National Institutes of Health. Invisible Disease: Depression. Bethesda, Md: National Institutes of Health; 2001. NIH publication 01–4591
2. Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system: epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94
3. Kessler RC, Avenevoli S, Ries Merikangas K. Mood disorders in children and adolescents: an epidemiologic perspective. Biol Psychiatry 2001;49: 1002–1014
4. Rupniak NM, Kramer MS. Discovery of the antidepressant and anti-emetic efficacy of substance P receptor (NK1) antagonists. Trends Pharmacol Sci 1999;20:485–490
5. Saria A. The tachykinin NK1 receptor in the brain: pharmacology and putative functions. Eur J Pharmacol 1999;375:51–60
6. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 1998; 281:1640–1645
7. Rupniak NM, Carlson EC, Harrison T, et al. Pharmacological blockade or genetic deletion of substance P (NK(1)) receptors attenuates neonatal vocalisation in guinea-pigs and mice. Neuropharmacology 2000;39: 1413–1421
8. Rimon R, Le Greves P, Nyberg F, et al. Elevation of substance P-like peptides in the CSF of psychiatric patients. Biol Psychiatry 1984;19:509–516
9. Berrettini WH, Rubinow DR, Nurnberger JI Jr, et al. CSF substance P immunoreactivity in affective disorders. Biol Psychiatry 1985;20:965–970
10. Rupniak NM, Williams AR. Differential inhibition of foot tapping and chromodacryorrhoea in gerbils by CNS penetrant and non-penetrant tachykinin NK1 receptor antagonists. Eur J Pharmacol 1994;265:179–183
11. Kramer MS. Substance P (NK1) receptor antagonists (SPAs) in patients with major depression. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii