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Key Words: paroxetine, PTSD, posttraumatic stress disorder, SSRI, selective serotonin reuptake inhibitor

Treatment of Posttraumatic Stress Disorder: The Impact of Paroxetine

By Jonathan R.T. Davidson, MD

ABSTRACT *~ The past decade has seen remarkable advances in our ability to treat patients with posttraumatic stress disorder (PTSD). In addition, we are now much more aware of the prevalence of PTSD in civilian populations, and treatment studies now reflect the broad spectrum of patients with PTSD. Findings of studies conducted with the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), mood stabilizers, and benzodiazepines suggest varying degrees of efficacy, with the MAOIs being particularly efficacious. However, the adverse-effect profiles of these agents, especially the TCAs and the MAOIs, limit their widespread use. The efficacy and tolerability of the selective serotonin reuptake inhibitors (SSRIs), paroxetine, sertraline, and fluoxetine, also have been demonstrated in clinical trials. Paroxetine is especially well studied in this regard, with demonstrated efficacy in men and women, in both short-term and long-term studies, and in combat veterans and civilians. Paroxetine also has been shown to improve quality of life, and to improve sleep disturbances, which can be remarkably disabling, in patients with PTSD. Emerging evidence also suggests that long-term treatment with paroxetine reverses the reductions in hippocampal volume and hypothalamic-pituitary-adrenal axis abnormalities associated with PTSD.* Psychopharmacology Bulletin. *2003;37(Suppl 1):76-88.*

INTRODUCTION

Until just a few years ago, it was widely believed that pharmacotherapy achieved little more than scratching the surface in the treatment of chronic posttraumatic stress disorder (PTSD). Initial studies in combat veterans yielded modest gains. Some studies were negative,[1,2] and others yielded meaningful, but limited, benefits.[3,4] Subsequently, we have learned that in broader-based populations of noncombat-exposed civilians, pharmacotherapy, particularly the selective serotonin reuptake inhibitors (SSRIs), can produce substantial therapeutic gains. In the first part of this report, an overview of the field is presented, and the remainder of the paper focuses on the knowledge gained from studies of paroxetine in PTSD and in novel animal and clinical models of this disorder.

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OVERVIEW OF PTSD

Posttraumatic stress disorder is a surprisingly common condition that affects at least 8% of the US population.[5] Much higher rates of PTSD are reported in other parts of the world, such as Ethiopia (15.8%), Israel (17.8%), Cambodia (28.4%), and Algeria (37.4%).[6] It has been estimated that within 20 years, motor vehicle accidents, war, and violence will be the third, eighth, and twelfth leading causes of disability worldwide after ischemic heart disease (first) and major depression (second),[7] which suggests that rates of PTSD also will increase dramatically.

Posttraumatic stress disorder generally follows a chronic course, and often, patients are not properly diagnosed for many years. It has been estimated that persons with PTSD experience approximately 20 years of active symptoms before diagnosis/treatment.[8] Quality of life, resilience, and normal stress-coping mechanisms also are compromised in persons with PTSD.[9]

A hallmark feature of PTSD is psychiatric comorbidity, especially depression and alcohol/substance abuse. Typically, it is the dysfunction associated with these psychiatric comorbidities that prompts patients to seek treatment. Patients with PTSD also frequently present with somatic complaints, such as severe disturbances in sleep (eg, insomnia, nightmares, sleep apnea), abdominal pain, symptoms of irritable bowel syndrome, headache, and fatigue. It therefore behooves physicians to recognize PTSD behind its many clinical masks. However, to do so always requires a high index of suspicion for current or past traumatic experiences.

The treatment challenges in PTSD therefore include, first, the ability to recognize this often masked disorder, second, the development of adequate clinical skills to obtain an accurate trauma history, which is often difficult because of concerns about stigma, shame, and difficulty with recall. Also, it must be remembered that obtaining a careful trauma history often takes time that is not readily available to physicians with busy practices. However, even inquiring about past or present untoward life events can be a sufficient first step in uncovering information that can lead to a diagnosis. Another clinical challenge is to treat the disorder and associated comorbidities effectively to full clinical remission.

PSYCHOPHARMACOLOGIC TREATMENT OF PTSD

Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Initial controlled trials in World War II and Vietnam veterans demonstrated that the tricyclic antidepressants (TCAs) amitriptyline[3] and imipramine[4] were more effective than placebo, and that the monoamine oxidase inhibitor (MAOI) phenelzine was particularly effective in 1 study.[4] These studies were of 8 weeks' duration, and both

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used effective maximal TCA and MAOI doses of 300 mg and 90 mg (phenelzine), respectively. A negative trial of desipramine showed no benefit in PTSD and mild benefit in depression.[2] It was possible that the short 4-week treatment period at a less than maximal dose may have had some bearing on the outcome of the desipramine trial.

The reversible, selective inhibitors of monoamine oxidase type A (RIMA) have been studied, with 2 placebo-controlled trials evaluating brofaramine in mixed-trauma populations. One study was largely negative,[10] although benefit was found on the Clinical Global Impression (CGI) score.[11] The second study was more positive than negative, especially in the subpopulation with the most chronic PTSD.[12] Although there has been one encouraging open-label study of moclobemide,[13] the RIMA drugs have not become established as credible treatment options for PTSD. Phenelzine is a highly effective compound, but the safety and tolerability challenges of this drug restrict its use, as is true for other irreversible MAOIs.

Selective Serotonin Reuptake Inhibitors

The SSRIs are considered first-line treatment of PTSD. In a meta-analysis of psychopharmacologic treatment of PTSD in which 5 different classes of drugs from 19 studies were considered, the SSRIs were shown to be more effective based on effect size than the TCAs, the MAOIs, carbamazepine, or the benzodiazepines.[14]

Sertraline. In the early 1990s, sertraline was evaluated in the treatment of PTSD and, on the basis of 2 positive studies conducted in noncombat veterans,[15,16] received approval as the first indicated treatment for PTSD. It is worth noting that a large trial in combat veterans was negative (Pfizer, unpublished data on file). A small, placebo-controlled study in Israeli combat veterans did demonstrate a modest advantage for sertraline, but this study was not adequately powered for the findings to be widely extrapolated to the clinical setting.[17] The findings of 1 particularly important study demonstrated the ability of sertraline to protect against relapse during continuation treatment. There were 5-fold lower rates of relapse or exacerbation in patients who were maintained on sertraline for 13 months, as opposed to patients who were switched to double-blind placebo after 9 months.[18] Long-term treatment has been reported to improve quality of life in patients with PTSD.[19]

Fluoxetine. Fluoxetine also has been studied in the treatment of PTSD, initially by van der Kolk and colleagues,[20] who demonstrated efficacy, which was more apparent in female survivors of violent trauma than in male combat veterans. This was a short-term study, with a high dropout rate. A second trial demonstrated the efficacy of fluoxetine.[21]

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Noteworthy in the study by Connor and associates[21] was the significant effect of fluoxetine on resilience, as well as its broad-spectrum effect on all PTSD clusters, quality of life, and daily function.[9] Of 2 major multicenter trials undertaken by the manufacturer, one was positive,[22] with the sample being predominantly composed of male combat veterans from European conflicts. A more recent study demonstrated continuation of benefit for fluoxetine over placebo, with relapse rates being 6% and 16%, respectively.[23] On the primary TOP-8 measure, statistically significant differences were noted at 3, 4 and 5 months, respectively, following discontinuation of the medication. The unusually long half-life of fluoxetine perhaps ensures that sustained benefit is maintained for a few weeks after the drug is discontinued, but that eventually clinical deterioration occurs.

Other Drugs

One early study found a good effect for thiopentone over placebo in a PTSD-like syndrome.[24] Recent studies have shown benefit for mirtazapine over placebo,[25] risperidone versus placebo,[26] and limited but potentially meaningful advantages for olanzapine in combination with an SSRI,[27] although 1 negative placebo-controlled trial of olanzapine alone also exists.[28] Finally, the mood stabilizer, lamotrigine, may hold promise on the basis of a small placebo-controlled trial.[1] However, outside of SSRI studies, little is known about the overall benefit or place of mood stabilizers, atypical antipsychotics, or other antidepressants in the management of PTSD. Of note, there has been 1 positive study of nefazodone versus placebo in combat veterans with PTSD.[29]

Acute Stress Disorder and Prevention of PTSD

Interesting studies have recently been completed to suggest that it may be possible to prevent the development of acute stress disorder in the immediate aftermath of trauma, which may be a prodrome or precursor of PTSD. One study of propranolol[30] has shown ability of the drug, when given for 10 days, to eliminate the development of physiological hyperreactivity at reexposure to reminders of the trauma 3 months post-event. However, rates of PTSD in the drug and placebo groups at 3 months were not different. In a population of septic shock survivors, hydrocortisone was associated with lower rates of PTSD at 3-year follow-up as compared with placebo.[31] Finally, in a group of children with acute stress disorder pursuant to severe burn trauma, 1 week of imipramine at 100 mg per day produced a high rate of response relative to the inactive hypnotic control, chloral hydrate.[32]

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EXPERIENCE WITH PAROXETINE IN PTSD

The findings of short-term and long-term clinical trials of paroxetine in the treatment of PTSD will be reviewed. In addition, the findings of other important work with paroxetine will be discussed in a) healthy volunteers, suggesting beneficial effects on affiliation and hostility, b) chronic treatment with paroxetine for 9 to 12 months in PTSD suggestive of restorative effects on hippocampal function and structure, and finally c) reference to recent work about the neurobiological effects of early-life adversity.

Clinical Trials of Paroxetine in PTSD

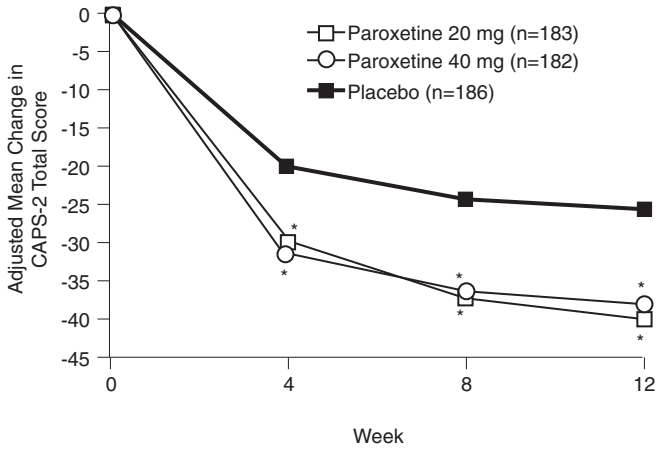
Three similarly designed studies have been completed in which paroxetine was compared with placebo, 1 of which was a fixed-dose study comparing 20 mg versus 40 mg[33] and the other 2 being flexible-dose studies (ranging from 20 to 50 mg/d).[34,35] A fourth study evaluated flexible doses of paroxetine during the course of 9 months' treatment (E. Vermetten, unpublished data).

Short-Term Studies.

Fixed-dose study. The fixed-dose study by Marshall and colleagues,[33] also 12 weeks in duration, found no difference between daily doses of paroxetine 20 mg and 40 mg, both of which were superior to placebo. The sample in this study was somewhat more depressed, with baseline

FIGURE 1

CAPS-2 SCORE CHANGES BETWEEN PAROXETINE 20 MG, 40 MG, AND PLACEBO



Change from baseline in the Clinician Administered PTSD Scale (CAPS-2) total score. Significant differences between paroxetine 20 mg or 40 mg versus placebo.

*P<.001

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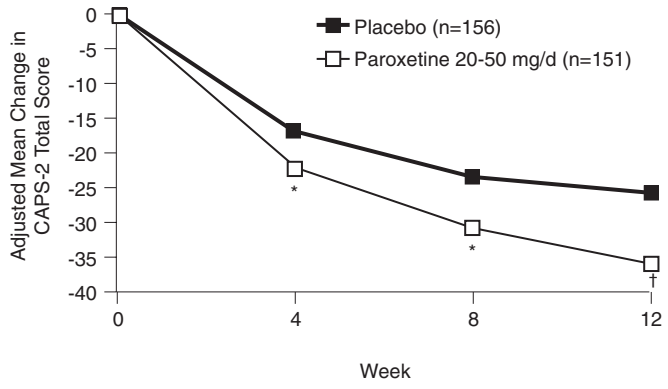
Montgomery-Asberg Depression Rating Scale (MADRS) scores of 24 to 25. Comorbid disorders were freely represented, especially depression, generalized anxiety disorder, and agoraphobia. As with the study conducted by Tucker and colleagues,[35] statistically significant differences between paroxetine and placebo were noted on the Clinician Administered PTSD Scale (CAPS) total score at weeks 4, 8, and 12 (Figure 1), in addition to the 3 symptom clusters of intrusion, avoidance/numbing, and hyperarousal. Response rates were 37% for placebo, 62% for the 20-mg dose, and 54% for the 40-mg dose of paroxetine. Uniform superiority for paroxetine was found on the self-rated Davidson Trauma Scale, with respect to both total score and symptom clusters, as well as on the TOP-8, the MADRS, and the Sheehan Disability Scale (SDS). Importantly, in patients with and without comorbid major depression, paroxetine was superior to placebo. Superior effect also was noted for men and women on the primary outcome measure. Outcome did not vary according to type of trauma, duration since onset of trauma (which was 15 years on average), or severity of baseline symptoms. The authors stress the impact of paroxetine treatment in this population of patients with moderately severe to severe PTSD.

Flexible-dose studies. In the first flexible-dose trial of paroxetine treatment of PTSD, Tucker and associates[35] reported significant advantage for paroxetine on the CAPS total score (Figure 2), as well as the

FIGURE 2

PAIRWISE COMPARISONS OF PAROXETINE VS PLACEBO



Change from baseline in the Clinician Administered PTSD Scale (CAPS-2) total score. Pairwise comparisons paroxetine versus placebo.

*$P<.05$; †$P<.001$
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reexperiencing, avoidance/numbing, and hyperarousal symptom clusters. Statistically significant differences between paroxetine and placebo emerged at week 4, and were sustained thereafter. As far as reexperiencing symptoms were concerned, significance emerged at week 12, whereas for the avoidant/numbing and hyperarousal clusters, significance was first noted at week 8. These drug effects were echoed on other measures, including the interviewer-assessed TOP-8 scale and the self-rated scales for PTSD and disability. Depressive symptoms were measured by means of the MADRS, and significant differences between paroxetine and placebo were observed in this dimension. It is noted that with baseline MADRS scores of 21, patients had mild to moderately severe major depression at baseline, reminding us of the significant issue of depressive comorbidity in PTSD.

One clinically useful way to interpret the findings of this study is to evaluate the proportion of patients who achieved response or full remission. Using a definition based on the CGI improvement scale, 59% of paroxetine patients responded compared with 38% of patients randomized to receive placebo. Remission rates were reported by the authors as being "nearly 30%" for paroxetine and "less than 20%" for placebo. The authors also commented on the high level of impairment in their sample, in which the baseline SDS rating was 17,[35] higher than that seen in panic disorder or generalized anxiety disorder. The type of trauma made little difference to outcome, in that paroxetine was superior to placebo for survivors of combat trauma, sexual assault, serious accident, or witnessing someone hurt or die. The greatest impact for paroxetine over placebo occurred among those patients who had witnessed trauma.

The third short-term study, which is currently unpublished, is a 12-week, flexible-dose comparison of paroxetine (20 to 50 mg) and placebo that evaluated 310 patients with chronic PTSD. Superiority was found for paroxetine on the CAPS total score, with a reduction in score on paroxetine that was 5.5 points greater than on placebo (P=.04), and on the DTS, with a difference of 7.3 points between treatments (P=.02). No difference was found on CGI-I-based response rates.[34]

Gender effects. In a pooled analysis of 1180 patients participating in the 3 paroxetine studies, Pitts and colleagues[36] assessed the differential effect of paroxetine treatment in men and women with PTSD. Paroxetine was significantly more effective than placebo (P<.001) in the treatment of PTSD, regardless of gender.

Improvement in sleep disturbance. In a pooled analysis of the 3 short-term paroxetine studies, Sheehan and colleagues[37] described the superiority of paroxetine over placebo at end point on nightmares, according to the DTS (P<.001) and a trend toward statistical signifi-

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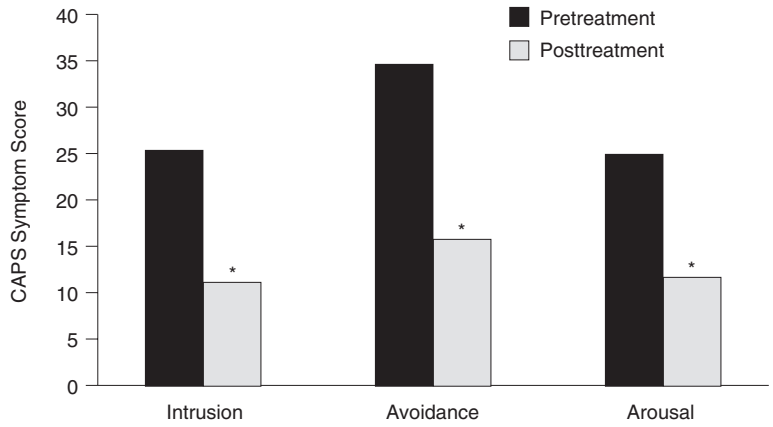
cance on the CAPS total score (P=.053). With respect to trouble falling or staying asleep, statistically significant differences were noted for paroxetine on both the CAPS (P<.001) and the DTS (P=.002). On the MADRS, the rating of overall improvement in sleep was significantly greater for paroxetine than for placebo (P=.002). Moreover, although treatment-emergent insomnia can be a problem with some SSRIs, no difference was observed in the incidence of this particular side effect between paroxetine (11.5%) and placebo (11.3%). Thus, among the SSRIs, paroxetine can certainly be distinguished by its therapeutic effect on initiating and maintaining sleep, on overall sleep time, and on nightmares related to the traumatic experience(s). Because these are often very vexing problems that sustain the illness to some degree, and often cause substantial disruption of relationships with patients' partners, the observation of improved sleep with paroxetine is a very welcome finding.

Long-Term Study. The efficacy of paroxetine in the long-term treatment of PTSD was assessed as part of a neuroimaging study in men and women with various trauma histories (E. Vermetten, unpublished data). Patients began open-label paroxetine treatment with doses of

FIGURE 3

CHANGES IN CAPS SYMPTOMS SCORE IN PATIENTS WITH PTSD OVER 9-MONTH OPEN-LABEL TREATMENT WITH PAROXETINE 20 MG TO 50 MG



Changes in Clinician Administered PTSD Scale (CAPS) symptoms score after 9 months of open-label treatment with paroxetine 20 mg to 50 mg in 23 men and women with posttraumatic stress disorder (PTSD)

*P<.001

E. Vermetten, unpublished data.

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10 mg with a forced titration to 20 mg after 4 days. The dose for patients who did not respond to the 20-mg dose was gradually titrated to no more than 50 mg. A total of 28 patients were enrolled, and 23 completed the 9-month study. Clinical efficacy was measured with the CAPS. Compared with mean baseline CAPS scores, paroxetine treatment resulted in a 54% improvement in end point scores ($P<.0001$). End point scores on each of the symptom clusters (eg, reexperiencing, avoidance/numbing, hyperarousal) also were significantly improved compared with baseline (Figure 3). Treatment with paroxetine also resulted in significant improvements over baseline in verbal declarative memory.

Related Studies with Paroxetine

Further studies have demonstrated that paroxetine is capable of attenuating hostility (negative affect), as well as promoting affiliative behaviors, and that the extent to which the drug induces these changes is proportional to plasma levels of paroxetine in healthy volunteers.[38] Although further studies are clearly warranted, these findings are of interest in the context of treating patients with PTSD.

The study conducted by Vermetten and colleagues (unpublished data) interestingly demonstrates that, after long-term treatment, paroxetine may be associated with a reversal of the structural changes in the brain that are associated with PTSD (ie, reduced hippocampal volume). In this population of men and women with chronic PTSD, overall hippocampal volume increased by 4.6% over baseline ($P=.005$) after a 9-month course of treatment. These findings are of substantial importance and speak to the necessity of maintaining treatment for chronic PTSD over a period of many months, if not years. On this, the data speak with one voice for all of the SSRIs.

Recent work in animal and clinical models of early-life trauma is of direct relevance to the better understanding of the neurobiology of PTSD. The findings of a series of studies in animal models of maternal separation and neglect have shown that compared with control animals, rat pups exposed to handling stress and maternal separation during critical, early developmental periods exhibit enhanced sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic systems, as demonstrated by exaggerated corticosterone and ACTH responses to a startle stimulus. Adult rats who were maternally deprived as pups also were more susceptible to stress than control animals and exhibited symptoms resembling depression and anxiety disorders.[39-41]

Paroxetine has been shown to eliminate or reduce anxiety-related behaviors and HPA axis responsiveness in maternally deprived rats after 21 days of administration.[42] Moreover, at least 21 days are needed to achieve reduction in paraventricular nucleus CRF mRNA in the

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maternal separation rat pup group. Interestingly, following withdrawal of paroxetine, hypothalamic CRF concentrations return to pretreatment levels in approximately 2 weeks (Plotsky, Nemeroff, unpublished data). Thus, these basic science studies cast a potential light on mechanisms of action of paroxetine and other antidepressants in PTSD, and provide a solid counterpart to the clinical database, which has established broad-spectrum efficacy for the drug in chronic PTSD. Whether paroxetine and other SSRIs may prevent the development of PTSD in subjects at risk is worthy of further investigation.

CONCLUSION

Five important goals of pharmacotherapy in PTSD consist of success in a) treating the full PTSD symptom complex, b) treating comorbid disorders, c) improving quality of life, d) restoring daily functioning, and e) strengthening resilience. Available data show that all can be accomplished with the SSRIs. There is a limited literature on predictors of response to selected drugs, the results of which are summarized in Table 1. We can say that there is good evidence for acute benefit and long-term effects in PTSD for paroxetine, sertraline, and fluoxetine, and that PTSD arising from any kind of trauma, including military combat, can be successfully treated with one or either of these drugs. Promising signs exist to suggest that early intervention may prevent PTSD, but more studies are needed in this regard.

During the past decade, substantial strides have been taken with respect to understanding the place of pharmacotherapy in PTSD. As far as

TABLE 1

PREDICTORS OF RESPONSE TO AT, BRO, SERT, AND PLACEBO IN PTSD[18,43,44]

DRUG*	PLACEBO
Depression (AMI)	Sexual trauma
Neuroticism (AMI)	Early response within 4 weeks†
Extent of trauma exposure (AMI)	
Concentration disturbance (AMI)	
Guilt (AMI)	
Somatic anxiety (AMI)	
Avoidance of discussing event (AMI)	
PTSD severity (BRO)	
Intrusive symptom severity (BRO)	
Avoidance severity (BRO)	
Early response within 4 weeks (SERT)†	

Predictors of response to amitriptyline (AMI), brofaromine (BRO), sertraline (SERT), and placebo in posttraumatic stress disorder (PTSD)*In all cases, better response occurred at lower levels of severity.
†Predictive of lack of relapse when sertraline later withdrawn after several months' continuation treatment.

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treating chronic PTSD is concerned, the SSRIs are appropriately established as the first line of therapy. Fluoxetine, sertraline, and paroxetine all are efficacious, with the paroxetine database being conspicuously the largest. Paroxetine has been shown to not only possess broad-spectrum efficacy, but to particularly enhance PTSD-related sleep disturbance, to work equally effectively in men and women, and to work well in survivors of many different types of trauma, including combat, sexual assault, and witnessing trauma to others. ✤

DISCLOSURE

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