

Patient-reported outcomes in post-traumatic stress disorder

Part II: Focus on pharmacological treatment

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Introduction

Exposure to traumatic experiences leads to a broad range of acute affective, cognitive, behavioral, and physiological symptoms in most affected individuals. This distress load may greatly vary in intensity. Fortunately, the majority of traumatized persons will

Post-traumatic stress disorder (PTSD) may be associated with long-lasting psychological suffering, distressing psychosocial disability, markedly reduced health-related quality of life, and increased morbidity and mortality in a subgroup of individuals in the aftermath of serious traumatic events. Both etiopathogenesis and treatment modalities of PTSD are best conceptualized within a biopsychosocial model. Pharmacotherapy may lay claim to a major role in the multimodal treatment approaches. Here we outline two different pharmacotherapeutic trends that aim to modify the encoding, consolidation, and rehearsal of traumatic memory in order to reduce the risk of PTSD immediately after trauma exposure on the one hand, and that endeavor to treat the clinical state of PTSD on the other. The theoretical rationales of both pharmacological strategies are the complex neurobiological underpinnings that characterize traumatic memory organization and clinical PTSD. Meanwhile, promising data from randomized controlled trials have been obtained for both approaches. Empirical evidence may inform clinicians in their clinical efforts for this special group of patients. The efficacy of several classes of drugs that have been investigated within a context of research should be evaluated critically and still have to stand the test of effectiveness in daily clinical practice. From a patient perspective, empirical results may serve as a psychoeducative guideline to what pharmacotherapeutic approaches may realistically achieve, what their risks and benefits are, and what their limits are in contributing to reducing the often major chronic suffering caused by serious traumatic events. Ethical issues have to be considered, particularly in the context of pharmacological strategies projected to prevent PTSD in the aftermath of traumatic exposure.

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recover within a certain period of time. In a subgroup of subjects, exposure to trauma, however, may cause long-standing emotional sequelae that are conceptualized as acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) in diagnostic terms.¹ PTSD is associated with major psychiatric comorbidity, serious psychosocial disability, significantly reduced health-related quality of life, and particularly in chronic courses, with a generally increased morbidity and mortality. From an etiopathogenetic perspective, ASD and PTSD may best be considered within a biopsychosocial model. Within this overarching theoretical context it has become evident that acute post-traumatic reactions after trauma exposure, any transition to acute stress disorder and PTSD, and especially chronic courses are mediated both by complex psychosocial, psychological, and neurobiological mechanisms.²⁻⁴ Regarding mental care for individuals with PTSD it has also become apparent that any exclusive psychological or pharmacological approach to this complex clinical challenge must face narrow constraints. Very often multimodal therapeutic strategies are required to effectively reduce the psychopathological load of a patient suffering from PTSD, to help him or her master the traumatic experiences, and foster psychosocial recovery. Therefore, any pharmacological approach has to be integrated into a setting of multimodal treatment.

Pharmacotherapeutic treatments established by empirical and clinical research so far may best be subdivided into approaches that, firstly, endeavor to reduce the risk of transition to PTSD after traumatic exposure, and that, secondly, treat particular PTSD-related syndromes. Former strategies refer to neurobiological mechanisms which mediate any traumatic experience to a consolidation of traumatic memory; they may be considered more specifically neurobiological hypothesis-driven. Latter strategies refer to prominent dysfunctions of neurotransmitter systems which characterize diagnostically established PTSD, but may be also prominent in other psychiatric disorders, such as depressive or anxiety disorders, that are often coexistent in the course of PTSD; therefore pharmacological effects in PTSD have to also be evaluated from a transdiagnostic perspective.

Pharmacological approaches to preventing PTSD after trauma exposure

In the line of secondary prevention, pharmacological tools attempt to mitigate the manifold processes

of encoding, consolidation, and rehearsal of traumatic memories activated by the traumatic event. These pharmacological approaches probably have major impact on the formation of traumatic memory only if they act within a relatively short period of some hours after trauma exposure.⁵ Several pharmacological strategies have been investigated to prevent noradrenergic overconsolidation of traumatic emotions in the amygdala, thereby maintaining a more favorable modulation of traumatic excitation by prefrontal cortical systems, reducing intrusive remembrances and thus stopping further consolidation of traumatic memory.⁶⁻⁸

As noradrenaline plays a central role in emotional memory encoding and consolidation from the very beginning of any traumatic exposition, and as noradrenergic hyperarousal may lead both to basic impairments of cognitive control and effective modulation of emotional excitement normally mediated by prefrontal systems, counteracting noradrenergic hyperactivity might be a promising first step to preventing a risky transition to subsequent traumatic stress.

Reduction of noradrenergic hyperactivity may pharmacologically be achieved by postsynaptic β -adrenergic and α_1 antagonism and by presynaptic α_2 agonism.⁹ Results of studies with the β -adrenolytic *propranolol* have been inclusive. Promising results of a first controlled trial by Pitman et al¹⁰ and of two uncontrolled studies^{11,12} could not be confirmed by a randomized, double-blind and placebo- and gabapentin-controlled trial in patients with trauma-induced injuries.¹³ Two RCTs in patients with severe burns were negative in proving any statistically significant advantage of propranolol versus placebo as regarding reduced risk of PTSD later on.^{14,15} The overall evaluation of the preventive strategy with early use of propranolol after trauma exposure is still considered delicate.¹⁶ There may be a potential indication in patients with pronounced signs of autonomic hyperactivity after trauma exposure and without coexistent serious somatic morbidity or injury. Gender-differential effects may exist.¹⁷ Further research work has to be done, however.

Inclusive results have also been found in studies examining the preventive efficacy of the α_2 -agonists *guanfacine* and *clonidine* that both pharmacologically reduce the release of noradrenaline from the presynaptic terminal into the synaptic cleft.⁸ The delivery of the α_1 antagonist *prazosin*, however, seems to dispose of a more promising preventive potential, as has been

shown in several randomized controlled trials (RCTs) in patients already suffering from PTSD.¹⁸⁻²² Prazosin's pronounced positive effect on trauma-related sleep disturbances and nightmares makes it a promising candidate also in prophylactic interventional studies.^{23,24} This indication, however, still requires proper pharmacological investigation.

There is overwhelming evidence of a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis in PTSD indicating low levels of cortisol as a possible personality-bound predisposing factor and probable risk factor of PTSD after traumatic exposure.²⁵ Glucocorticoids are crucially involved in the regulation of memory and have a differential impact on memory consolidation, memory retrieval, and working memory. Its suppressive effect on recurrent intrusive sensation-based trauma memories might be considered as one decisive step to restrain any overconsolidation of traumatic memory. A delivery of stress-related doses of hydrocortisone, therefore, may be justified as another promising preventive strategy.²⁶ Several RCTs have confirmed a major efficacy of *hydrocortisone* in various serious somatic illnesses with high risk of PTSD (eg, acute respiratory distress syndrome, septic shock, heart surgery and subsequent intensive care.²⁷⁻²⁹ Beyond the context of intensive care units early use of hydrocortisone has also been found preventive both after military and civil traumata in first RCTs.³⁰⁻³²

γ -Aminobutyric acid (GABA)-ergic inhibitory control seems to be crucially involved in any precise regulation of consolidation, expression, and extinction of emotional, ie, traumatic conditioning.^{33,34} From clinical and experimental studies that established a profound disruptive effect of *benzodiazepines* (BDZ) on fear memory consolidation^{35,36}; one might consider their use in early states of post-traumatic processing. BDZ show strong stress-reducing and anxiolytic effects by dampening noradrenergic and glutamatergic hyperactivity, and thus might effectively counteract overconsolidation of trauma memory. This reasonable hypothesis, however, could not be confirmed in clinical RCTs; on the contrary, early use of benzodiazepines may even increase the later risk of PTSD.^{37,38} BDZ may induce typical anterograde amnesia that may be counterproductive in further processing. They may facilitate retrieval of trauma-related memories, simultaneously suppressing neutral information, thus being detrimental to the restorage of trauma memories after reactivation and negatively in-

terfering with the formation of newly acquired extinction memories.³⁹ In addition, BDZ may further reduce the cortisol response of the HPA axis.⁵ From a clinical point of view any use of BDZ as a routine preventive approach after trauma exposure, particularly any longer-lasting use, should be considered only with caution and reservation.⁴⁰

Uncontrollable pain during and following the trauma must be considered an independent condition that increases the risk of PTSD.⁴¹ Endogenous opiates play a major role in post-traumatic processing of pain. They reduce the intensity of pain perception and counteract panic affects triggered by noradrenergic hyperactivity. On the other hand, however, high levels of opiates may negatively interfere with processes of reality-based learning and memory. Early and adequately dosed exogenous *opiates* after traumatic burns,^{42,43} serious trauma-related injuries,⁴⁴ and during intensive care treatment⁴⁵ may probably mediate a secondary preventive efficacy with respect to later PTSD risk. It still has to be investigated whether early applied opiates may deliver a general prophylactic effect regarding later PTSD beyond this special pain-related effect.⁴⁶

Serotonin modulates noradrenergic reactivity and autonomous arousal. It has impact on HPA-axis functioning. It generally mediates inhibitory effects both on neuronal activity and plasticity. A well-balanced serotonergic neurotransmission is basic a precondition for flexible reality orientation and adequate reaction. Any prolonged and uncontrollable stress as in traumatic situations may lead to serotonergic dysfunction.⁴⁷ So far, *serotonergic antidepressants* have been investigated only rarely in their potential PTSD prophylactic effect. Early use of *escitalopram* after several military and civil trauma was found ineffective in a controlled comparison with placebo and cognitive behavioral interventions in the Jerusalem Trauma Outreach and Prevention Study.⁴⁸ Moderate prophylactic effects were demonstrated for *sertraline* in a small RCT with children after serious burns.⁴⁹ Empirical data are still insufficient to properly evaluate the preventive approach with SSRIs.

At first sight, within a medical model approach it seems to be highly plausible and responsible-minded to take every effort to reduce the risk of transition to a probably seriously debilitating psychological and psychobiological condition diagnosed as PTSD after a shattering trauma exposure. Any medical decision has to take into account several issues, however. First and

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foremost, a doctor has to assess whether any planned intervention in this indication refers to a well validated empirical data basis confirming that the intended intervention will reach the therapeutic or preventive aim with a certain probability at all, and its risk:benefit ratio is within an ethically justifiable range. The doctor has to guarantee that the person affected by the acute trauma is also in a psychological condition to be able to provide informed consent. The doctor also has to consider any alternative treatments or prophylactic measures. And in addition, the doctor is well advised to look at what public opinion is regarding this very intervention, as any controversial debate might have a major impact on the patient's mind as well. Keeping these preconditions in mind, any doctor will face several delicate problems in this situation. First-aid responsibility for persons shortly after a traumatic event in most cases means that they are being treated according to the principles of emergency medicine. Very rarely, the doctor will also carry out preventive duties in an explicit way. Both psychological and psychophysiological reactions shown by the traumatized person may still be in the range of a normal response to an extraordinarily frightening situation, eg, rape or violent assault. In most instances it is neither possible to properly assess the person's special and individual risk to progress to an acknowledged medical condition called PTSD, nor, as a rule, to address a person in the acute aftermath of a trauma who is able to give her/his well-informed consent to interventions that might be of some acute and/or of some preventive help. Even with the best medical approach and intention, the doctor may only refer to an empirical database that makes some pharmacological tools possible or likely candidates for early preventive interventions. The strength of available evidence underlines that some drugs may mediate some positive effects by altering the autonomic hyperarousal and emotional distress related to trauma and traumatic memories. The database having been established so far, however, is still insufficient to correctly assess the proper preventive potential of any of these drugs regarding the incidence of later PTSD.⁵⁰⁻⁵⁴ On an empirically informed level of assessment one has to keep in mind that several psychological preventive strategies are also far from being conclusive in their efficacy to reduce the risk of PTSD after trauma exposure and their acceptance by affected patients in an emergency setting.^{55,56} Although all pharmacological tools that have been investigated in the indication

of potentially preventive effects have been well tolerated without any serious side effects, a particular caveat has been brought up in public opinion: drugs altering memory might also alter the core feeling of personal identity. And regaining and re-establishing identity is of paramount importance to any traumatized person. A controversial ethical debate has been conducted on this topic in recent years, mainly focussing on the prophylactic use of propranolol after traumatic events.⁵⁷⁻⁶⁴ Serious concern has been expressed that substances such as propranolol might affect factual recall of a traumatic event. The available experimental and clinical data underline that only emotional distress associated with a traumatic experience or traumatic memory is being modulated, eg, by propranolol, and thus preventing overconsolidation of traumatic memory but leaving the factual memory unaltered.^{65,66} This eventual incidence, however, cannot be ruled out completely. The same line of argumentation has to be considered when reflecting on the mechanism of action of substances like hydrocortisone, which first and foremost suppresses the rehearsal process of traumatic memory.²⁶ This should definitely to be respected in the case of any prophylactic use of BDZ.³⁵ In the light of this debate and of available evidence-based data and considering the fact that most persons in an acute post-traumatic affective and cognitive state are not able to give their informed consent, any premature recommendation for a general use of these substances as prophylactic tools should be retained. This cautious position should advise patients in their expectations and guide doctors in their actions.

Pharmacological approaches in the treatment of post-traumatic stress disorder

Any pharmacological treatment of PTSD may be justified by the manifold neurobiological dysfunctions, especially in various neurotransmitter systems, high rates of psychiatric comorbidities, frequent chronic courses, and often only partial responses to empirically validated psychotherapeutic interventions. There are basic principles, however, that have to be considered in the pharmacological treatment of patients with PTSD:

- securely established therapeutic alliance
- drugs supplemented to standard psychotherapeutic treatment
- systematic reflexion on conscious and unconscious meanings of pharmacotherapy

- frequent problems of noncompliance
- syndrome-based selection of pharmacological agents
- consistent evidence-based treatment of any psychiatric comorbidities
- potential risks regarding serious side effects, abuse, suicidality
- frequent nonresponse or only partial response to standard doses.

Pharmacological research in diagnostically established PTSD so far has mostly followed the notion that major pharmacological tools with some approved efficacy in other related psychological disorders such as depressive or anxiety disorders might also deliver some benefit in PTSD as well. More or less all major classes of psychopharmacological drugs have been investigated in the indication of PTSD as well. Therefore, it must come as no surprise that attempting to modify the complex neurobiological underpinnings of PTSD with rather nonspecific pharmacological strategies will often produce less than optimal results. Overall, existing empirical data mostly refer to studies of acute short-term treatment lasting only for some weeks. Pharmacological long-term treatment, on the other hand, has been investigated only rarely in a systematic way. In interpreting empirical results one should keep in mind that rather a moderate criterion of reduction of baseline symptoms by some 30% has been selected in the majority of studies.

Serotonergic antidepressants

Serotonergic antidepressants, above all *selective serotonin reuptake inhibitors* (SSRIs), are among those psychopharmacological drugs that have been investigated most comprehensively in the indication of PTSD. The theoretical rationale refers to major serotonergic dysfunctions underlying many PTSD symptoms. There exist a great many RCTs that have significantly favored SSRIs (*fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine*) in comparison with placebo, but not unanimously. In respect to the overall efficacy of SSRIs in the treatment of PTSD, two controversial positions are being held^{3,23,67-69}:

- On the one hand, a systematic review conducted by the influential Institute of Medicine⁷⁰ generally called into question the efficacy of SSRIs in *war veterans* with chronic courses of PTSD. A consensus was reached that this subgroup not only responds rather

poorly to pharmacological, but to psychotherapeutic interventions as well. War veterans with shorter duration of combat-related PTSD seemed to respond to SSRIs more favorably. The issue of SSRIs for this special subgroup of PTSD patients is still under debate and open for further evaluation.³

- On the other hand, trials that investigated the efficacy of SSRIs in *civil trauma-related PTSD* mostly showed positive results and, in general, underlined major effects on the central symptom clusters of trauma-related intrusive memories, avoidance, and autonomic hyperarousal. The effect sizes regarding each single symptom cluster varied from trial to trial. So far, no statistically significant difference has been established that would speak in favor of any single SSRI. Doses of SSRIs used in these trials were in line with those normally used in trials for depressive disorders. In comparison with the rates of response or remission usually found for this indication, the corresponding rates in the treatment of PTSD were remarkably lower. As a rule, treatment periods lasted from 5 to 12 weeks. There are only a few long-term trials up to 24 weeks that demonstrated a consistent superiority of SSRIs to placebo on the one hand, and a continuous and steady improvement in all three PTSD symptom clusters throughout the whole trial period on the other hand.⁷¹

Good efficacy of *venlafaxine ER* was found in two RCTs.^{72,73} Some promising results were noted in an uncontrolled naturalistic study investigating *duloxetine* in the treatment of male patients with therapy-refractory PTSD.⁷⁴ *Mirtazapine* was not found to be significantly superior to placebo in a RCT, both mirtazapine and placebo presenting remarkable effect sizes each, however.⁷⁵ In another study mirtazapine was equivalently effective in comparison to sertraline.⁷⁶ There is only one open trial with *trazodone* showing promising results.⁷⁷ Both mirtazapine and trazodone may present a profile of favorable effects as regards PTSD-related sleep disturbances.

The partial 5-HT_{1A}-agonist *bupirone* may show some positive effects on symptoms of intrusion and autonomic hyperactivity, but less on symptoms of avoidance.^{78,79} In addition, bupirone may also potentiate the effects of SSRIs.⁸⁰ *Bupropion SR* was not significantly superior to placebo in a RCT.⁸¹

There are some older controlled trials with irreversible (phenelzine) and reversible *monoamine oxidase*

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(MAO) inhibitors (brofaromine, moclobemide) that demonstrated some promising results and generally seemed to be superior to the effects found in other trials with *tricyclic antidepressants* (amitriptyline, imipramine, desipramine). Presumably due to the generally lower efficacy of tricyclics and the more unfavorable spectrum of side effects, both of tricyclics and MAO inhibitors, these drug classes are being evaluated as second- or third-line treatment ranking after SSRIs and venlafaxine ER as first-line treatment in PTSD.⁸² Patients may realistically expect that serotonergic antidepressants will relieve the load of distress related to PTSD core symptoms to a moderate degree. The factual rates of remission, however, are significantly lower than those usually found in the treatment of depressive disorders. This empirical observation particularly applies to chronic courses of PTSD. SSRIs and venlafaxine ER may contribute to a better health-related quality of life and may improve PTSD-related disability and functional impairment, but the empirical data on this topic are far fewer than on matters of clinical efficacy. In all, this pharmacotherapeutic approach is secure and well tolerated, but, may cause some problems of additional anxiety and agitation in the beginning phase of treatment due to a mild serotonin syndrome. At least from a theoretical perspective, pharmacotherapy has to be projected as long-term treatment and should always be combined with evidence-based psychological treatments.^{83,84}

Mood stabilizers

At least from a theoretical point of view anticonvulsants used as mood stabilizers may promise some positive effects in the treatment of PTSD. There might be expected a favorable impact on symptoms of irritability, anger, aggression, and impulsivity that often accompany the course of PTSD. Underlying modification of GABAergic and glutamatergic neurotransmission may be assumed as theoretical explanation of these effects. Furthermore, special anti-kindling effects may be discussed. Whereas most open studies with anticonvulsants (carbamazepine, oxcarbazepine, valproate, lamotrigine, gabapentin, topiramate, tiagabine, and phenytoin) showed some encouraging results, data from RCTs with these mood-stabilizers were overall disappointing. Evaluation of the present state of empirical data underlines moderate effects on PTSD core symptoms at

most. So far no clear evidence has been established for any anti-kindling effect. And it is still in debate whether there are special effects on anger, aggression, and impulsivity so frequently associated with PTSD.⁸² From a meta-analytic standpoint that also assessed pooled data drawn from available studies, topiramate surprisingly turned out to be rather a potent substance in the treatment of PTSD,⁸⁴ a finding that awaits further validation. In all, patients may take some profit from taking anticonvulsants; a much higher rate of major and sometimes serious side effects has to be considered, however.

Antipsychotics

A series of RCTs with atypical antipsychotics (olanzapine,⁸⁵ risperidone⁸⁶⁻⁹⁰) suggested an additional encouraging pharmacotherapeutic approach in the treatment of PTSD core symptoms, especially improving symptoms of involuntary intrusive trauma memories and dampening distressing symptoms of autonomic hyperarousal. It may be of major importance that these substances may also significantly reduce an overall prevailing attitude of general mistrust and hypervigilance so frequently associated with chronic courses of PTSD. Quetiapine is also widely used for the frequent PTSD-related sleep disturbances. Major dysfunctions in dopaminergic neurotransmission may justify this antipsychotic strategy either as monotherapy or add-on therapy usually in combination with SSRIs. But this add-on strategy may fail in chronic courses of PTSD resistant to pre-treatment with SSRIs, as one RCT with risperidone demonstrated.⁹¹ Although atypical antipsychotics are much less likely than classical antipsychotics to cause extrapyramidal side effects, these may induce substantial weight gain, dyslipidemia, and elevated blood glucose. The problem of metabolic syndrome associated with long-term-use of atypical antipsychotics has raised major public health concerns. Aripiprazole and ziprasidone may be less burdened with these side effects. But even with these substances there may be some serious adverse interactions, eg, with SSRIs, as one RCT with sertraline and ziprasidone detected.⁹²

Benzodiazepines

The only RCT with benzodiazepines conducted so far pointed out that benzodiazepines were not able to decisively improve PTSD core symptoms.⁹³ Indication of

benzodiazepines in the treatment of PTSD should be carefully reflected and considered only for the short term at most. A potential impairing effect on further post-traumatic processing must be respected (see above). It has still to be elaborated whether *GABA_A*-agonists such as *zolpidem*, *zopiclone*, or *zaleplone* may be superior to benzodiazepines in the indication of PTSD-related sleep disturbances. One first RCT with *eszopiclone* showed promising results.⁹⁴ Several surveys demonstrate that in respect to the scarce and sobering empirical data as regards the efficacy of benzodiazepines in PTSD, the well-known problems in long-term use and the general concerns associated with post-traumatic processing one must be worried by the still major prescription rates of benzodiazepines for PTSD.⁹⁵ The acute anxiolytic and sedative effects of benzodiazepines may be welcomed both by patients and doctors alike because they may deliver the illusion of a prompt solution of a complex subjective and objective problem whereas actually impairing an adequate processing of painful traumatic experiences.

Opiates/opiate antagonists

Endogenous and exogenous opiates during or immediately after trauma exposure may mediate some protective effects (see above). Opioid-ergic drugs used during clinical states of PTSD and particularly in chronic courses may show differential effects. On the one hand, the opiate antagonists *naloxone/naltrexone* may sometimes trigger major symptoms of opioid withdrawal after trauma exposure and following PTSD.⁹⁶ On the other hand, these very same opiate antagonists may be found helpful in interrupting persisting dissociative states of trauma-induced depersonalization and derealization.^{97,98} In general, without a very stable therapeutic alliance and a well-established compliance opiate antagonists should not be frankly prescribed. Particularly patients with PTSD and comorbid opiate dependence may face an incalculable and even lethal risk when stopping these antagonists abruptly and resuming opiates again in states of relapse.

Experimental substances

Stress-related doses of *hydrocortisone* used immediately after trauma exposure may mediate a protective effect regarding the risk of later PTSD (see above).

Hydrocortisone might also be a potential option in the treatment of PTSD due to its inhibiting effect on the intrusive rehearsal of traumatic memories.²⁶ A methodologically well-designed crossover study in a very small sample of patients with chronic PTSD after a terroristic attack demonstrated confirming effects in accordance with the hypothesis.⁹⁹ The α_1 antagonist *prazosin* refers to an empirically well-established evidence of efficacy in improving PTSD-associated sleep disturbances and nightmares and additionally contributing to an overall reduction of PTSD core symptoms.¹⁰⁰⁻¹⁰² Patients may draw major benefit from this special strategy. They should also be informed about the subjective effects of prazosin, in most cases reducing the highly distressing and tormenting quality of nightmares and generally altering dream contents in the direction of positive trauma mastery. The many ethical concerns with respect to the use of memory-modulating substances as possibly PTSD-preventive interventions may be considered more or less invalid in the case of diagnostically established PTSD, particularly with a chronic course of illness. Any debate on loss or disruption of self identity has to take into account that it is chronic PTSD itself that mediates the most disastrous impact on psychological and psychosocial identity. And substances like prazosin or propranolol are justified as proper treatment tools if there is sufficient strength of evidence.^{103,104}

Critically assessing the efficacy of the various psychotherapeutic approaches to PTSD may disclose some major limitations as have analogously been reported for the several pharmacological strategies.⁶⁶ Searching for substances that might be favorably supplemented in order to support these psychotherapeutic endeavors has been a topic in recent research. The two *NMDA antagonists D-cycloserine* and *D-serine* have been proven to significantly contribute to the effects of exposition training in anxiety disorders.¹⁰⁵ Results from corresponding trials in PTSD have been inclusive so far,^{106,107} but indicate an interesting therapeutic potential that may be explored in further research.¹⁰⁸

Conclusion: general empirical evaluation of pharmacotherapeutic approaches in the treatment of PTSD

It is of paramount importance to inform patients that pharmacological tools are well compatible with psychotherapeutic approaches. They should be instructed that

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drugs may significantly improve distressing symptoms of PTSD, but they don't do the painful work of mastering traumatic experiences. However, they may decisively contribute to this endeavor. Patients should be told what benefits they may realistically expect from taking these pills, and what side effects they are likely going to encounter during the treatment. The doctor should put every effort into maintaining good compliance and should openly address any patients' complaints regarding the recommended medication.

Most systematic reviews and meta-analyses consider SSRIs as first-line treatment of PTSD.^{23,69,109-115} There exist positive results as regards acute and long-term treatment. SSRIs seem to mediate a broader spectrum of therapeutic effects than tricyclics, and seem to be better tolerated than both tricyclics and MAO inhibitors. SSRIs may significantly reduce PTSD core symptoms and may markedly improve anxiety and depressive disorders frequently associated with PTSD. Overall effect sizes of SSRIs, however, have to be judged as moderate. From a long-term perspective a predominate symptom suppressive effect has to be outlined, any withdrawal of medication demonstrating a still high risk of relapse. In comparison with SSRIs, serotonin-norepinephrine reuptake inhibitors (SSNRIs, particularly venlafaxine

ER) are based on fewer empirical data, but may be of comparable efficacy. SSNRIs, noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, and serotonin antagonist and reuptake inhibitor (SARI) trazodone are considered as second-line treatment. Atypical antipsychotics (olanzapine, risperidone) indicate quite a promising profile of therapeutic effects that has to be further explored, however. Atypical antipsychotics, together with mood-stabilizers, are being used first and foremost in add-on strategies. Benzodiazepines should be used only in a well-considered short term.

As a rule, pharmacological treatment of PTSD has to be projected as long-term therapy, acute treatment lasting from some 6 to 12 months at the minimum, chronic PTSD requiring, however, much longer periods of treatment. From the perspective of a biopsychosocial model, many good theoretical arguments may be found for the combination of pharmacotherapy and psychotherapy. The empirical basis for these combined treatment strategies is still scarce, however.¹¹⁶ Several pharmacological tools may have demonstrated efficacy in research settings, but must still prove their effectiveness within contexts of usual care for patients with PTSD and several other psychiatric and somatic comorbidities and frequent chronic courses.^{8,82} □

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Resultados percibidos por el paciente en el trastorno por estrés postraumático
Parte 2: Foco en el tratamiento farmacológico

El trastorno por estrés postraumático (TEPT) puede asociarse con un sufrimiento psicológico de larga duración, una perturbadora incapacidad psicosocial, una marcada reducción de la calidad de vida relacionada con la salud y un aumento en la morbilidad y mortalidad en un subgrupo de individuos como consecuencia de acontecimientos traumáticos graves. La etiopatogenia y las modalidades terapéuticas del TEPT son mejor conceptualizadas dentro del modelo biopsicosocial. La farmacoterapia puede demostrar un papel principal en las estrategias de tratamiento multimodal. Este artículo resume dos tendencias farmacoterapéuticas diferentes dirigidas a modificar la codificación, consolidación y repetición de la memoria traumática para reducir el riesgo de TEPT inmediatamente después de la exposición al trauma. Además se revisan los esfuerzos para tratar la sintomatología del TEPT. Los fundamentos teóricos de ambas estrategias farmacológicas son las complejas bases neurobiológicas que caracterizan la organización de la memoria traumática y de los síntomas del TEPT. Por otra parte, se ha obtenido información prometedora en ensayos controlados randomizados para ambas aproximaciones. La evidencia empírica puede informar a los médicos respecto de los esfuerzos clínicos para este grupo especial de pacientes. Se debe evaluar críticamente la eficacia de varias clases de fármacos que se han estudiado en el contexto de la investigación y que todavía tienen que superar la prueba de la eficacia en la práctica clínica diaria. Desde la perspectiva del paciente, los resultados empíricos pueden servir como una orientación psicoeducativa respecto a lo que los enfoques farmacoterapéuticos puedan realmente lograr, a cuáles son sus riesgos y beneficios, y a cuáles son sus límites en la contribución a la reducción del frecuente y principal sufrimiento crónico causado por acontecimientos traumáticos graves. También deben considerarse los aspectos éticos, especialmente en el ámbito de las posibles estrategias farmacológicas para prevenir el TEPT como consecuencia de la exposición traumática.

Résultats rapportés par les patients dans l'état de stress post-traumatique
2e partie : traitement pharmacologique

Chez un sous-groupe de personnes, l'état de stress post-traumatique (ESPT) peut être associé à une souffrance psychologique de longue durée, une incapacité psychosociale éprouvante, une qualité de vie liée à la santé considérablement diminuée et une morbi-mortalité augmentée, dans les suites d'événements traumatiques sévères. Le modèle biopsychosocial est le meilleur moyen de représenter à la fois l'étiopathogenèse et les modalités thérapeutiques de l'ESPT. Le traitement médicamenteux revendique un rôle central dans l'approche multimodale du traitement. Nous présentons ici deux tendances thérapeutiques pharmacologiques différentes qui visent à modifier l'encodage, la consolidation et la répétition de l'événement dans la mémoire traumatique afin, d'une part de diminuer le risque d'ESPT immédiatement après l'exposition au traumatisme, et d'autre part de s'efforcer de traiter l'état clinique de l'ESPT. Les théories de ces deux stratégies s'appuient sur des bases neurobiologiques complexes qui caractérisent l'organisation de la mémoire traumatique et l'ESPT clinique et bénéficient, entre-temps, de données prometteuses issues d'études contrôlées randomisées. Les médecins peuvent être informés par des données empiriques dans leurs efforts pour traiter ce groupe particulier de patients. Les classes médicamenteuses dont l'efficacité a été analysée dans un contexte de recherche doivent être évaluées sérieusement et montrer encore leur efficacité dans la pratique clinique quotidienne. Du point de vue du patient, les résultats empiriques pourraient servir de directive psychoéducative pour ce que les traitements pharmacologiques peuvent réellement réaliser, pour leurs risques et bénéfices et pour leurs limites en termes de diminution de la douleur chronique souvent majeure provoquée par des événements traumatiques graves. Les questions éthiques doivent être prises en compte, particulièrement dans le contexte des stratégies médicamenteuses de prévention de l'ESPT dans les suites d'une exposition à un traumatisme.

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