Propranolol in Post-Traumatic Stress Disorder

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Contributor: Łukasz Szeleszczuk, Dawid Frączkowski

Propranolol, a non-cardioselective β1,2 blocker, is most commonly recognised for its application in the therapy of various cardiovascular conditions, such as hypertension, coronary artery disease, and tachyarrhythmias. However, due to its ability to cross the blood–brain barrier and affinity towards multiple macromolecules, not only adrenoreceptors, it has also found application in other fields. For example, it is one of the very few medications successfully applied in the treatment of stage fright.

Keywords: propranolol ; anxiety ; stage fright ; PTSD

1. Post-Traumatic Stress Disorder (PTSD)

Individuals who are exposed to life-threatening trauma, such as wartime combat, assault, rape, car accidents, natural disasters, man-made traumas, or worldwide pandemics [1], are at risk of developing PTSD. People with PTSD suffer from severe psychological distress as a result of having to relive their trauma repetitively through intrusive flashback memories [2][3][4]. Other severe symptoms accompany these memories, such as emotional numbing, avoidance of trauma-related stimuli, and a constant state of increased arousal and hypervigilance [5][6][7]. Cognitive dysfunction has been identified in PTSD and linked to impaired traumatic memory processing [8], elevated psychiatric symptom severity, and functional disability [9]. The ability of the hippocampus (HPC, the main location for memory storage) to control the memory of traumatic events is also found to be dysfunctional [10]. Anxiety and sleep difficulties are some of the debilitating and persistent symptoms of PTSD [11]. PTSD patients usually have heightened resistance to extinction learning [12]. This disorder has been linked to an increase in the frequency of suicide behaviours, such as suicidal thoughts, plans, or actions, as well as other mood disorders and anxiety symptoms [13][14]. According to paediatric studies, children with burns who do not receive adequate pain management may develop PTSD [15][16]. Children with PTSD often exhibit avoidance behaviours, increased arousal, flashbacks, and nightmares [17].

In its fifth edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the American Psychiatric Association updated the PTSD diagnostic criteria in 2013 [18]. The DSM-5 diagnostic criteria list exposure to actual or threatened death, significant injury, or sexual abuse as the numerous specific triggers for PTSD. Regardless of its cause, the ensuing disturbance results in clinically substantial distress or a deficiency in the person's capacity for social interaction, employment, or other critical areas of functioning. DSM-5 merely requires that the disturbance persist for longer than a month and eliminates the distinction between acute and chronic phases of PTSD [19]. However, at least a third of those who initially develop PTSD continue to face symptoms for three years or longer [11].

PTSD affects about 8% of the population in the United States [20][21]. Females are more than twice as likely as males to develop PTSD following a traumatic event [22]. The Food and Drug Administration (FDA) has approved only two medications to treat it (paroxetine hydrochloride and sertraline hydrochloride), both with limited efficacy [20][21]. Trauma-focused psychotherapies enable PTSD remission. The advantages of such treatments decline over time [23].

The hypernoradrenergic state is associated with the pathophysiology of PTSD [24]. Noradrenaline (norepinephrine, NE) and adrenaline, which cause stress, are often found in higher concentrations in PTSD patients [19]. It is believed that adrenaline helps memory consolidation and contributes to the reoccurrence of PTSD symptoms [25]. Given the high and positive correlation between cerebrospinal fluid (CSF) NE levels and the severity of PTSD symptoms [24], one possible explanation is that traumatic memory reactivation in a patient with severe PTSD may result in the release of a higher level of NE than in a patient with non-severe PTSD. Furthermore, PTSD patients' HR or blood pressure (BP) have increased in reaction to stressful signals, demonstrating conditioned fear responses [26][27]. The discovery that memories were pliable and changeable rather than fixed triggered a series of studies that totally altered how PTSD is treated today [10].

2. The Medical Use of Propranolol

2.1. Cardiovascular

Although propranolol was first developed to treat angina pectoris, its use in other cardiovascular conditions, such as hypertension, cardiac arrhythmias, and myocardial infarction, was soon recognised [28][29][30][31].

Despite many new generation cardioselective beta-blockers being now available, propranolol continues to be used in specific conditions. For example, propranolol has been found to be as effective as carvedilol on left ventricular volume and function after primary coronary stenting in acute myocardial infarction [32]. Barton et al. assessed the efficacy and safety of high-dose propranolol for the management of supraventricular tachyarrhythmias (SVTs) in infants (N = 287) [33]. Bonten et al., in a meta-analysis including 31 studies, found that propranolol significantly decreased platelet aggregation [34]. Propranolol has also been extensively used for the management of essential hypertension [35].

2.2. Psychiatric

According to a meta-analysis, propranolol may be useful in the treatment of anxiety disorders caused by unsettling memories, notably PTSD [36]. Furthermore, propranolol is useful in lowering emotional arousal [37], eradicating stage fright [38], and alleviating anxiety-related cognitive dysfunction [39].

2.2.1. Stress

It is important to consider propranolol's potential as a preventative treatment for chronically stressed individuals [40]. Propranolol reduced anxiety-like behaviours while also increasing resilience to a following stressor [41]. An oral dose of 80 mg propranolol lowered the rise in HR and systolic BP brought on by stress to 49.9% and 8.3%, respectively, as opposed to 61.0% and 17.4% with placebo. Additionally, propranolol markedly reduced the skin's temperature increase on the trunk [42].

PTSD

Propranolol has also shown promise for the treatment of chronic PTSD [43]. This β-AR antagonist was found to block memory reconsolidation in healthy humans in a fear conditioning test [44], and studies have reported successful propranolol-induced reconsolidation disruption that lasted at least one month and was resistant to fear reinstatement [36]. Fear memory reconsolidation is the process by which reactivation by exposure to the conditioned stimulus (CS) or an unconditioned stimulus (US) makes memory traces labile, thereby triggering transient protein destabilisation that can be modified by pharmacological and behavioural interventions for several hours after memory reactivation [45]. Fear memories can be updated with new information thanks to the reconsolidation process [45].

The first clinical trial in PTSD patients was conducted by Brunet et al. [46]. It was discovered that providing chronic PTSD patients (N = 19) 60 mg of long-acting oral propranolol followed by 40 mg of short-acting oral propranolol significantly decreased physiologic response to the memory one week later. Oral propranolol given 1 h before retrieval of the US reduced subsequent fear responses and disrupted connections between all CSs and the US [47]. The effects of propranolol administered one hour before exposure to emotionally charged or neutral storylines were investigated by Cahill et al. [48]. In comparison to the control group, participants who received propranolol remembered fewer emotional details. Propranolol administered within the first 6 h after a traumatic event significantly reduces the likelihood of developing PTSD [49][50]. This drug appeared to be effective during the reconsolidation time window, which lasted approximately 6 h and enabled the original memory to be updated with new protein synthesis [51][52][53]. The physiological reactivity and HR of those who received propranolol 4–12 h after the trauma reportedly improved [54]. Moreover, administering propranolol three times per day for a week after a trauma minimised the onset of PTSD symptoms [49]. In a randomised clinical trial [55] with "pre-reactivation propranolol therapy", PTSD participants (N = 60) who actively recalled their traumatic event under the influence of propranolol once a week for up to six weeks showed a significant decrease in symptom scores (PTSD symptom improvement = 36%) compared to those who received pre-reactivation with the placebo (PTSD symptom improvement = 13%). Chronic propranolol treatment may be more beneficial in alleviating PTSD symptoms, according to certain human studies [36][50]. Additionally, in patients with severe PTSD symptoms (the PTSD Check List ≥ 65; PCL-S ≥ 65) before treatment, PCL-S and the Beck Depression Inventory-II (BDI-II) scores continued to decline three months after the end of treatment in the propranolol group, while they increased in the placebo group [56]. Brunet et al. discovered that the physiological response to trauma reactivation was low even at four months following the therapy [57]. Although this therapy has been referred to as "forgetting therapy", its goal is to help patients separate their emotions and worries from their memories rather than making them forget their physical experiences. Even five months after starting to take propranolol, the advantage was still evident: the flashbacks completely stopped occurring, and the

emotional reaction to the nightmares was greatly reduced. In a case report, it has been described that the treatment with propranolol resulted in a decrease in alcohol use and an improvement in the patient's quality of life [19].

Following memory reactivation, this API can decrease the identification of emotional pictures, according to additional research utilising functional magnetic resonance imaging [58]. A propranolol-mediated decrease in sympathetic tone in the period surrounding re-exposure can lead to changes in the subjective qualities of emotional memories, which is compatible with propranolol's anxiolytic effects [38][57][59][60][61]. A meta-analysis of healthy humans found that a single memory reactivation session combined with propranolol medication lowered the strength of negatively valenced emotional memories [36]. Propranolol can disrupt a fear memory that is specific to the reactivated CS when administered during CS retrieval-induced reconsolidation [47]. Furthermore, the propranolol-induced suppression of fear memory reconsolidation retrieved by the US was effective for remote fear memory and exhibited a reasonably long-lasting effect (at least two weeks) [47]. In humans, the unconditioned stimulus-based memory retrieval interference procedure with propranolol can permanently reduce the fear response and prevent the return of fear for all CSs [47]. Numerous follow-up studies of propranolol administration after reactivation in humans convincingly confirmed attenuated emotional responses while also demonstrating that it preserved declarative memory, i.e., knowledge of CS–US contingencies remained unaffected [62][63][64][65][66][67][68]. A case series found that providing 40 mg of propranolol shortly after reactivation decreased PTSD symptoms [69]. Six brief trauma reactivation sessions under the influence of propranolol resulted in considerable PTSD symptom improvement in three other independent open-label studies. Patients who all developed PTSD as a result of the industrial disaster in Toulouse in 2001 were compared; 8% in the control group lost their diagnosis, compared to 86% of treated patients [59].

Propranolol therapy seems to be a potentially safe and effective therapeutic option for children with PTSD symptoms [70]. In a pilot trial, Famularo et al. [71] investigated the advantages of propranolol therapy for children with PTSD who had suffered severe physical and sexual abuse. While using propranolol, children reported a considerable improvement in their PTSD symptoms.

Moreover, propranolol may alter visuospatial processes associated with the resolution of traumatic intrusions in those with chronic PTSD [43]. After taking propranolol, HR drops were associated with improved Perceptual Organisation (PO) performance, which may point to peripheral and central β-adrenergic blockade effects on cognition, specifically during visuospatial processing and visual attention in PTSD [72]. Additionally, propranolol decreased diastolic BP, which was associated with less severe PTSD symptoms [43]. In addition, propranolol may improve Processing Speed (PS) performance in PTSD patients as compared to placebo [43]. In combination with extinction training and when administered soon after trauma, propranolol may be most effective at reducing long-term fear [73].

2.2.2. Anxiety

The majority of mental health disorders are anxiety-related [74], and they have significant psychological, social, and financial implications [75]. A common anxiolytic drug with minimal effects on cognition is propranolol hydrochloride [76][77]. The use of propranolol to mask the physical symptoms of anxiety is well established [19]. This medicine reduces the physiological symptoms of anxiety, such as BP, changes in HR, respiration rate, and skin conductance [76]. According to Granville-Grossman and Turner's [78] cross-over study, patients with anxiety states were evaluated to be significantly better after two weeks of propranolol treatment compared to two weeks of placebo. Patients with chronic anxiety were treated with propranolol at a dose of 160 mg daily. After two weeks of treatment, propranolol severely decreased the physical aspects of anxiety, and it also significantly relieved other symptoms including shortness of breath, chest pains, and weakness that had some association to beta stimulation [79]. Experimental findings suggest that administering propranolol soon after retrieving an emotional memory can cause post-reactivation amnesia, which is the attenuation of the memory's later expression [80]. It has been demonstrated that propranolol has an acute effect on fear-potentiated startle responses [80]. Additionally, studies on propranolol have indicated that it can alleviate less stressful conditions such as exam anxiety [81][82][83], stage fright [38], performance anxiety in musicians [84], and fear of surgery [85][86].

Stage Fright

For decades, beta blockers such as propranolol have been used to treat situational anxiety such as stage fright and exam- or interview-related anxiety [38][82]. Propranolol has been used in the clinic for its short-term effect in performance anxiety, including test taking and oral presentations [76]. Stage fear no longer causes any physical performance barriers thanks to beta blockade, which also results in the removal of the common dry mouth [38]. Considering that physical anxiety symptoms usually worsen the patient's anguish, providing the patient 40 mg of propranolol 1 h before a performance may be quite helpful [87]. According to experienced music critics, the level of musical performance substantially improves after taking this medication [38].

Social Anxiety Disorder (SAD)

The strategy for reducing anxiety during exposure treatment is to target psychophysiological arousal with propranolol administration, which makes anxiety during exposure more tolerable and may increase the chances of effectively coping with the feared situation. In patients with SAD, propranolol was combined with one session of exposure [88]. On the second day, there was a decrease in anxiety.

Fear of Public Speaking

Fear of public speaking is a 'performance only' subtype of SAD, characterised by extreme fear in, and avoidance of, public speaking situations, without more general social impairment as a result of anxiety [89]. It is one of the most widespread fears, and it can lead to missed educational, social, and professional opportunities [90]. Administration of propranolol during reconsolidation mitigated public speaking anxiety [89]. Regardless of participant body mass, 40 mg of propranolol was found to be an effective dose for fear neutralisation [91], and the medicine may be administered up to 1 h after reactivation [68].

2.2.3. Phobias

Propranolol has been demonstrated to be effective in reducing anxiety in patients with dental phobia [92] and arachnophobia [64].

Fear of Dental Extraction

It has been shown that extractions raise the risk of developing chronic anxiety for dental surgical operations, acute types of dental anxiety (i.e., dental phobia), and post-traumatic stress symptoms [93]. One month after having their wisdom teeth surgically removed, a small percentage of patients, between four and eight percent, experience heightened dental trait anxiety or even PTSD symptoms [94][95]. Propranolol may be used to treat dental trait anxiety because traumatic memories appear to be crucial in its maintenance and severity [96]. Propranolol has a beneficial impact on dental anxiety and lessens the storage of fear memories. Furthermore, propranolol has the capacity to inhibit 'memory reconsolidation' (that is, it blocks the process of storing a recently retrieved fear memory) [93]. It has been observed that, as compared to placebo, 80 to 120 mg of oral propranolol significantly reduced self-reported states of anxiety during injection of a local dental anaesthetic [92].

Arachnophobia

Soeter and Kindt [64] used a live tarantula to reactivate a naturalistic fear memory in subjects who were afraid of spiders. This 'memory reactivation' was promptly followed by oral propranolol administration. Participants who received propranolol + reactivation showed significant reductions in their fear of spiders, and were able to touch or even hold spiders for at least a year after the intervention. On the other hand, those who received placebo + reactivation or propranolol alone showed no alterations in their fear. The fear levels of control participants remained stable, while reactivation + propranolol participants achieved immediate and significant reductions in their fear of spiders. These control conditions show that the fear reduction cannot be explained by propranolol's general fear-dampening effect or by simply being exposed.

In addition, the eye-blink startle reflex was used to test the reaction to a loud noise combined with exposure to a fear-relevant stimulus (for example, photographs of spiders). Twenty-four hours after the drug's administration, the behavioural reaction to the fear memory was completely erased. Furthermore, retrieval methods failed to reactivate the fear response [44][61][97].

However, 36 arachnophobic people participated in a double-blind, placebo-controlled trial conducted by Elsey and Kindt [98], who also used a reactivation procedure. They discovered a trend for better results in the placebo group, who showed larger improvement in phobic behaviour scores than the propranolol group [98].

2.2.4. Autism Spectrum Disorder (ASD)

Propranolol may be beneficial to people who suffer from emotional, behavioural, and autonomic dysregulation (EBAD). This medicine also may help children with ASD and EBAD improve their therapy outcomes by alleviating symptoms related to autonomic dysregulation and/or hyperarousal. A considerable reduction in aggression, organic brain dysfunction [99][100][101], and anxiety disorders [102][103] has been reported in adolescents with ASD [104]. Moreover, propranolol was found to be effective in reducing self-injurious behaviours (SIBs) in people with ASD [105]. There is also some evidence that the use of propranolol may result in significant improvements in EBAD, the symptomatology of ASD, with a focus on cognitive performance and neural correlates and the management of behaviour, predominantly for aggression and SIBs

[106]. Propranolol's anxiolytic impact via the autonomic nervous system may be beneficial in people with greater physiological anxiety [107].

Individuals with ASD showed improvements in verbal problem solving [108][109], semantic processing [110], and working memory (WM) when administered propranolol [111]. Moreover, propranolol was found to improve functional connection in people with ASD [112][113]. These findings also point to propranolol's ability to support cognitive processing. Greater associative processing and subnetwork integration may be obtained by regulating NE. As a result, people with ASD may have improvements in attention-shifting, sensory processing, language communication, and social information processing [112]. In addition, increases in nonverbal communication [114] and reductions in hypersexual behaviours [115] were noted. These benefits were found in studies that used a 40 mg propranolol dosage, with only one study utilizing a low dose of 20 mg [115]. Propranolol may be a potential therapy choice for patients with ASD who have complex symptoms [106].

2.2.5. Other Psychoses

When benzodiazepines, anticonvulsants, and major tranquillizers failed to manage adult patients' explosive rage outbursts and episodic belligerence, propranolol was used successfully [99]. The use of this medicine has been documented in case reports for the treatment of agitation in organic patients [116], aggressive behaviour following acute brain damage [117], and postencephalitic psychosis [118]. According to reports, the medication is also effective in treating acute postpartum psychosis [119]. Propranolol administered in 30–38 mg doses daily was found to significantly reduce uncontrollable rage outbursts in a study of 30 children and adolescents with organic brain dysfunction [101].

2.3. Other Uses

Other than those described above, therapeutic applications of propranolol include, but are not limited to, migraine prophylaxis [120], cluster headache prevention [121], and pheochromocytoma [122]. Propranolol has been also used in the treatment of various rare vascular diseases, including hereditary haemorrhagic telangiectasia, von Hippel–Lindau disease, paraganglioma syndrome, cerebral cavernous malformations, angiosarcoma, and tuberous sclerosis [123]. Oral propranolol administration seems to be an effective method to minimise the development of sight-threatening choroidal effusion after glaucoma surgery [124] as well as an effective and safe medication in the treatment of primary hyperhidrosis [125].

3. Mechanism of Action of Propranolol in the Treatment of PTSD

By decreasing retrieval of fear memories via the dorsal medial prefrontal cortex (dmPFC) and improving contextual safety learning via the HPC, beta-blockade can stop the recurrence of fear [126]. Furthermore, a reduction in diastolic BP was positively linked with a decrease in the severity of PTSD, confirming the anxiolytic effects of blockers via peripheral and central noradrenergic processes [127]. Stress-related NE release and compensatory downregulation β-adrenergic receptors (β-ARs) in the heart and peripheral vessels appear to play a role in these physiological effects [43]. The MAPK and JAK/STAT3 pathways may be among the biochemical pathways by which propranolol (and NE itself) influences aversive learning and memory processes, albeit this understanding is still in its early stages. According to Johansen, LeDoux, and colleagues, the MAPK pathway interacts with postsynaptic β-adrenergic signalling in the lateral nucleus of the amygdala (AMG) to modify the formation and consolidation of fear memories [128]. Other research has connected NE (and propranolol) with IL-6 signalling, and one group suggested that infusion of the inflammatory cytokine IL-6 into the basolateral amygdala (BLA) in rats may alter fear extinction learning, possibly through the JAK/STAT3 pathway [129][130].

The sympathetic nervous system's excessive activity is a defining characteristic of PTSD [131][132][133][134]. The postulated therapeutic mechanism of action of propranolol is that beta-blockers prevent the binding of adrenaline and NE at the receptors (beta-1 and beta-2 for adrenaline, beta-1 for NE) [19]. The noradrenergic system is of key importance in modulating memory processes, and it has been found that stimulation of β-ARs facilitates the reconsolidation of emotional memory [135]. One of the promising strategies to treat PTSD is to pharmacologically block memory reconsolidation of the traumatic event [136]. Propranolol has been shown to interfere with memory reconsolidation [137]. Both memory formation and memory dissociation from emotional reaction may be inhibited by propranolol [19]. Propranolol selectively blocks protein synthesis, thereby prohibiting fear memory reconsolidation while leaving declarative memory unaffected [44]. This medicine crosses the blood–brain barrier and interferes with the neurobiological cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element binding protein (CREB) cascade that is involved in the reconsolidation of destabilised fear memories by acting on β-ARs in the AMG, a brain area crucial for emotional regulation [128][138][139]. The increased release of NE, activation of β-AR, and higher surface expression of GluA1-containing α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), particularly the surface expression of extrasynaptic GluA1 in the lateral amygdala (LA), all contribute to the fear reactivation-induced preservation of fear memories. By altering the stability of GluA1 in LA, propranolol successfully prevented the changes brought on by NE and reactivation

[140]. The AMG's ability to activate and store memories is thought to be modulated by stress hormones, which propranolol is known to inhibit [141]. Propranolol can help with stress-related symptoms via affecting AMG-dependent memory reconsolidation and peripheral noradrenergic signalling [41]. Preclinical studies have shown that a single dose of propranolol administered immediately after an intense stressor (exposure to a predator/predator scent, electric shock) blocks subsequent expression of anxiety-related behaviour [142][143][144], possibly by impairing the consolidation of the stressful experience. Propranolol reaches its highest systemic concentration 75 min after intake [56]. Additionally, long-term use of propranolol may successfully lower tonically increased NE signalling in PTSD sufferers (i.e., those who would no longer benefit from acute propranolol paired with exposure therapy) [73].

Propranolol has been shown to reduce fear expression by modifying network-related activity and diminishing the reactivation of the initial traumatic memory trace [145]. Propranolol's effects were demonstrated to be centrally mediated, with impaired fear memory retrieval that was context specific, contrary to an anxiolytic effect or alterations in generalised fear, according to behavioural controls [145]. The acute effects of propranolol are linked to: (1) decreased functional connectivity within and between the HPC, prefrontal cortex (PFC), and AMG regions; (2) decreased activity in the LA and infralimbic area (ILA); (3) changes in memory trace reactivation in the dorsal dentate gyrus (dDG) and BLA; and (4) changes in the correlation between memory trace reactivation in the anterior cingulate area (ACA), LA, and dorsal cornu ammonis 3 (dCA3) and freezing [145]. While enhanced dorsolateral PFC activity during the anticipation of unpleasant stimuli is connected with reduced symptom severity and better visuomotor PS in PTSD, greater AMG activation has been linked to slower visuomotor PS [145]. Despite propranolol's ability to block access to the fear memory engram in the HPC during memory retrieval, it is probable that decreased activity in the ILA reduced extinction learning [12]. The dorsal HPC (dHPC) is essential for learning and memory associated with exploration and spatial navigation [146]. Propranolol's acute effect on fear behaviour could be attributed to a decreased reactivation of the contextual components of fear memory in the dHPC [145]. The fear memory reactivation rate of encoding cells in the ACA was positively correlated with freezing levels in the control group, but not with propranolol, demonstrating that the ACA plays a role in fear memory encoding and retrieval, as well as mediating propranolol's effects [145]. In addition, the ILA, which has fear-dampening/proextinction effects, becomes positively correlated with the ventral CA3 (vCA3) under propranolol [145]. The ventral HPC (vHPC) is thought to harbour a memory component of emotional valence, and, therefore, a greater inhibitory influence of the ILA on the vCA3 could influence fear retrieval. Disruption of the connection between these regions, which contain different components of the memory trace, may play a role in the behavioural effect [145].

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