A review of atypical antipsychotics and their utility in post-traumatic stress disorder

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ABSTRACT

Post traumatic stress disorder (PTSD) is a chronic and debilitating mental illness. Atypical antipsychotics are often utilized for treatment of PTSD despite the limited data. The purpose of this article is to review published clinical trials of atypical antipsychotics used in the treatment of PTSD. Certain patients may benefit from therapy with an atypical antipsychotic, particularly for those with hyper-arousal or re-experiencing symptom clusters. At this time, guidelines suggest against the use of risperidone as augmentation therapy in patients with PTSD. Data are only available for olanzapine, quetiapine, and aripiprazole; however, data were conflicting, not very robust, and studies had limited sample sizes and narrow demographics. It is important to provide proper patient education and weigh the risks versus benefits of therapy with an atypical antipsychotic as metabolic side effects are well documented.

KEYWORDS

post traumatic stress disorder, antipsychotics, treatment

INTRODUCTION

Post traumatic stress disorder (PTSD) is a chronic and debilitating mental illness. Following a traumatic life event patients experience symptoms clustered into three areas: hyper-arousal, avoidance/numbing, and intrusive recollection of the traumatic life event or re-experiencing.[1] Lifetime prevalence of PTSD in adult Americans is estimated to be 6.8%.[2] This varies between genders with men at 3.6% and at women 9.7%.[3] Rates are understandably higher in the veteran population due to their combat exposure. Service members previously deployed to Iraq and Afghanistan have an estimated PTSD prevalence rate of 13.8%.[4]

Treatment guidelines clearly put selective serotonin reuptake inhibitors (SSRIs) as first line treatment for PTSD. Unfortunately, even when treated with SSRIs, response rates rarely exceed 60% and less than 30% achieve full remission.[5,6] This leaves many clinicians seeking alternative treatments and augmentation strategies. Psychotic symptoms can also occur with PTSD and may be an indicator of a more severe symptomatology. Atypical antipsychotics have broad effects on serotonin, norepinephrine, and dopamine receptors that can have positive effects on depression, anxiety, and cognition. This broad range effects make them a possible alternative option for PTSD treatment augmentation.

Atypical antipsychotics are often utilized for treatment of PTSD despite the limited amount of well-designed clinical trials supporting their use.[7] A study published in 2007 found that patients with PTSD accounted for over 40% of off-label atypical antipsychotic prescriptions within the Veterans Administration (VA), and that 19.4% of patients diagnosed with PTSD were receiving an atypical antipsychotic.[8] The following will serve as a review of published clinical trials of atypical antipsychotics utilized for the treatment of PTSD and how this is reflected in the treatment guidelines.

METHODS

PubMed was used for the literature search. Medical Subject Headings (MeSH) terms for each atypical antipsychotic were searched in combination with the MeSH term for PTSD. Results were limited to clinical trials of humans (see tables 1-4). One case series of aripiprazole was included in the results to compliment the data found in the few other clinical trials performed with aripiprazole.

RISPERIDONE

Risperidone is the most studied of the atypical antipsychotics for the treatment of PTSD. The majority of trials have been small in size and used risperidone as augmentation to patients' current therapy. There have been only two published trials of risperidone being used as monotherapy for PTSD. The first, published in 2005, included 26 Croatian war veterans diagnosed with psychotic PTSD.[9] They received open label risperidone 2-4 mg/day over six weeks of inpatient treatment. Significant reductions were reported in the primary outcome of Positive and Negative Symptoms Score (PANNS) score as well as secondary outcomes of PTSD-Interview scores and Clinical Global Impression (CGI) scores. Another small (n=20) randomized controlled trial studied women with PTSD who had been victims of sexual abuse or domestic violence.[10] Intervention was placebo or risperidone over a 12-week period. Authors reported the risperidone group saw a significant reduction in Post-traumatic Stress Disorder Scale-8 scores in comparison to the group's baseline.

A total of six trials have been published with risperidone being studied as augmentation in the treatment of PTSD, three of which reported positive results. Two open-label trials with less than 25 patients reported positive results when using risperidone to treat irritability and intrusive thoughts in both combat related PTSD and PTSD related to childhood abuse in women.[11,12] A study conducted by the VA was the first to show a significant reduction in Clinician-Administered PTSD Scale (CAPS) scores. At a single VA study site, 65 patients were randomized to risperidone titrated to 3 mg daily or placebo.[13] At the end of the 16-week study, the risperidone group saw significantly greater reduction in CAPS, CAPS-D, and PANNS-P scores.

Other trials with risperidone have had conflicting results. A trial by Hamner et al. in 2003 looked at risperidone for treatment of comorbid psychotic symptoms in patients with PTSD.[14] Over a five-week period, patients treated with risperidone had statistically significant reductions in PANNS total scores, but despite reductions in both groups CAPS scores, no difference was seen between treatment and placebo groups. Another trial in a civilian population failed to show any benefit when risperidone was added to sertraline over an eight-week period.[15]

The Veterans Affairs Cooperative Study published by Krystal et al. is the largest randomized controlled trial of any atypical antipsychotic being used for the treatment of PTSD.[16] This study included 247 veterans with SSRI treatment resistant, combat related PTSD. Veterans were highly symptomatic at baseline with average CAPS scores of 78.2 (14.8 SD), Montgomery–Åsberg Depression Rating Scale (MADRS) scores of 23.4 (8.2 SD) and Hamilton Anxiety Scale (HAM-A) scores of 19.4 (7.8 SD). Groups were randomized to risperidone titrated up to 4 mg/day or placebo. After six months of treatment no difference was seen in ratings of PTSD, anxiety, depression, positive or negative symptoms, sleep, or quality of life. This study had strong validity with its multiple measures, low cross-site variability, and long study duration. The results demonstrated that the small benefit risperidone may provide in chronic PTSD is likely outweighed by its metabolic adverse effects. It is important to note that these results may not be applicable to women, civilians, or use of other atypical antipsychotics.

OLANZAPINE

Olanzapine has been used in the treatment of PTSD for psychotic symptoms such as hallucinations, delusions, and bizarre behaviors. The available literature for olanzapine is limited, and sample sizes are small making it difficult to extrapolated results to a generalized population.

Butterfield et al. performed a pilot study looking at olanzapine vs. placebo for the treatment of PTSD.[17] Ten patients were randomly assigned to olanzapine and five patients to placebo over a period of ten weeks. The sample included men and women, and both civilian and military trauma. This study found no evident difference in response between the olanzapine and the placebo groups. A detailed analysis of specific PTSD symptom clusters were also included and no difference was observed between olanzapine and placebo.

Petty et al. conducted an eight-week open-label trial of olanzapine in 46 male veterans with chronic combat-induced PTSD.[18] Treatment with olanzapine was associated with statistically significant improvement on the primary outcome measures of improvement in CAPS score and CGI from baseline. CAPS total score at baseline was 85.17 compared to 59.78 ($p < 0.001$) at week

eight. Patients also showed significant improvement on secondary outcome measures as well. The scores on the HRSD (Hamilton Rating Scales for Depression) and HAM-A decreased by 30% and 31% respectively. Improvement in CAPS symptom cluster subscale was also noted from baseline, with improvement in intrusive (31%), avoidant (31%), and hyper-arousal (28%) symptoms being significant. There was a high dropout rate (16 patients, constituting 34% of the sample) primarily due to metabolic side effects, and it is difficult to extrapolate this data to civilian trauma or women as the sample group were all male combat-veterans.

A 2012 study by Carey et al. is the only randomized, double-blind, placebo-controlled study looking at olanzapine as monotherapy in PTSD.[19] The study design utilized parallel groups and flexible doses over eight weeks. Mean baseline CAPS score was greater than 75 with no baseline severity between groups (p = 0.686). The olanzapine group demonstrated significantly greater improvement in CAPS total score with a mean change of -35.86±19.85, a 57.7% improvement) compared to placebo group (-19.29±28.77, a 23.7% improvement) from baseline to week eight (p=0.018). The study also demonstrated separation of the olanzapine group from the placebo group by the end of week 4 (p=0.014), and dose had been maintained for two weeks. The study notes that treatment with olanzapine resulted in improvement in all three symptom clusters of PTSD on the CAPS, however only improvement in avoidance and numbing were statistically significant at week four (p=0.005) and maintained at week eight (p=0.004). This study included both men and women and looked solely at civilian trauma, primarily domestic and criminal violence.

Stein, Kline, and Matloff looked at olanzapine as adjunctive treatment in SSRI-resistant combat-related PTSD.[20] In this double-blind, placebo-controlled study, all participants were male and had chronic military-related PTSD. They also were deemed to be minimally responsive to 12 or more weeks of SSRI therapy, with four or more weeks being at maximally tolerated doses. Of the 19 patients that completed the study, five were taking fluoxetine (median dose 40mg/day), seven were taking paroxetine (median dose 40mg/day) and seven were taking sertraline (median dose 200mg/day). Patients continued on their SSRI and were randomly assigned to placebo or 10mg olanzapine as adjunctive therapy. CAPS scores for both groups at baseline were severe (>80) and both groups exhibited depressive symptoms and sleep problems. The olanzapine group had a significantly greater reduction in PTSD symptoms, sleep disturbance, and depressive symptoms compared to placebo.

QUETIAPINE

Available evidence for quetiapine is small, but it is often added as adjunctive treatment for sleep in patients with PTSD. It has sedating properties, but it is also suggested that due to its actions on 5-HT2 receptors (similar to trazodone) and α-1 receptors (similar to prazosin) it may be an effective agent to reduce nightmares and re-experiencing while sleeping.

Hamner et al. published the first trial using quetiapine as an adjunctive treatment in PTSD.[21] In a six week open-label trial, 20 patients were enrolled and treated with a flexible dose of quetiapine ranging from 25-300 mg with a mean dose of 100 ± 70 mg. Authors reported a significant reduction in PTSD symptoms, depressive symptoms, and psychopathology. Using data from this same trial, researchers later reported patients had an improvement in sleep disturbances when treated with quetiapine.[22]

Ahearn et al. published another open-label trial using quetiapine as augmentation for patients on a stable dose of an SSRI. Fifteen patients were followed over an eight week period.[23] Authors reported a 42% overall improvement in patients CAPS scores and significant improvements in each domain of hyper-arousal, re-experiencing, and avoidance.

Byers et al. compared the long-term effectiveness and safety of quetiapine and prazosin in treatment of PTSD related nighttime symptoms.[24] The study was a prospective cohort study performed by retrospective chart review of 237 veterans. Investigators evaluated short-term effectiveness as documented in the chart and long-term effectiveness based upon adherence. Short-term effectiveness was similar for prazosin and quetiapine, but patients prescribed prazosin were significantly more likely to continue their therapy (48.4% vs. 24%; P < 0.001) making it more effective long-term. Patients in the quetiapine group were also more likely to discontinue treatment due to adverse effects (34.9% vs. 17.7%; P = 0.008). Authors recommended use of prazosin first line due to superior long-term efficacy and lower incidence of adverse effects.

ARIPIPRAZOLE

Aripiprazole has a somewhat novel mechanism of action and was found to have less metabolic side effects compared to quetiapine and olanzapine.[25] Aripiprazole was given FDA approval for schizophrenia, monotherapy or adjunct to a mood stabilizer in bipolar I disorder,

adjunct therapy for MDD, and psychomotor agitation in relation to schizophrenia, bipolar disorder, and autism. The hyper-arousal symptom cluster of PTSD can often manifest as irritability, agitation, or aggression leading to a possible place in treatment for aripiprazole.

A case series by Lambert (2005) looked at five cases of combat-related PTSD that were managed, in part, by aripiprazole.[26] All cases were of veterans of the Global War on Terrorism (GWOT). Hyper-arousal and sleep disturbances tend to be the most prominent symptoms in this patient population. Four of the five cases showed improvement of symptoms with aripiprazole 15 or 30mg in combination with either sertraline or cognitive behavioral therapy. One patient experienced hyper-excitation on aripiprazole 15 mg, and elected to discontinue medications and only pursue psychotherapeutic interventions instead.

A 16-week, open-label trial by Mello et al (2008) sought to evaluate the efficacy of aripiprazole as monotherapy for treatment of PTSD.[27] Thirty-two patients were enrolled with 23 patients completing the study. The patients were all victims of civilian trauma. The study defined a 30% decrease on CAPS score as "response criteria." Doses of aripiprazole ranged from 3.75-15mg/day. Baseline CAPS scores: 20 people had scores >80 (extremely severe), eight scored between 60-79 (severe), three scored between 40-59 (moderate), and one scored between 20-39 (mild). Re-testing during the post-treatment period revealed, six patients that remained extremely severe, six were severe, eight were moderate, seven were mild, and five were subclinical (CAPS < 19). Although the study does not disseminate what level of severity the CAPS scores were in people who discontinued the study, they did state that those who discontinued had more severe depressive symptoms at baseline and primarily dropped out due to side effects. When utilizing the mean CAPS scores, the study did meet their outcome, with a 38% reduction in mean CAPS scores. Although this study does show some improvement in certain individuals, it is difficult to say which people actually received benefit. This study supported aripiprazole's role as adjunct therapy more than as an agent for monotherapy.

Richardson et al. (2011) performed a retrospective chart review of patients who received at least 12-weeks of adjunctive aripiprazole.[28] Twenty-seven patients were identified to have military-related PTSD with co-morbid major depression. Participants were prescribed aripiprazole after demonstrating partial response to their existing antidepressant and/or partial or minimal response to other antipsychotic augmentation strategies. The study discovered significant decreases between baseline and each of the three follow-up appointments on both the Beck's Depression Inventory (BDI) and the PTSD Checklist (PCL). At the final follow-up the decrease in PCL scores for re-experiencing, avoidance, and hyper-arousal were all statistically significant ($p=<0.05$). This study supported previous studies in veterans by finding efficacy with augmentation of aripiprazole, however the study also noted that there was a lower overall response rate in patients with severe co-morbid depression.

Finally, a more recent open-label pilot study by Youssef et al. (2012) looked at male and female veterans with chronic PTSD who had suboptimal response to antidepressants.[29] The 12-week trial enrolled ten participants to look at the safety, tolerability, and efficacy of aripiprazole monotherapy for the treatment of PTSD. Aripiprazole was well tolerated, with the main side effect being weight gain (n=6, mean weight increase 6.5 lbs). Two patients experienced akathisia, but this was corrected with a dose decrease and consequent symptom resolution. Statistically significant decreases in the mean scores were found on all PTSD measures: CAPS, SPRINT (Short PTSD Rating Interview), TOP-8 (Treatment Outcome PTSD Scale), and DTS (Davidson Trauma Scale) ($p=<0.05$ for all measures). For CAPS, the primary outcome of decrease in total CAPS score was achieved as well as the outcome for re-experiencing. On the self-rated DTS, significant decreases were also found for symptoms of re-experiencing and hyper-arousal. Decreases in cluster C symptoms were not statistically significant. This study had a very small sample size, but it provides some evidence supporting the possible use of aripiprazole for the treatment of PTSD.

OTHER ATYPICAL ANTIPSYCHOTICS

The remaining atypical antipsychotics had either no literature available regarding their use in PTSD, or the literature that is available may be restricted to a case report. Often times, the case report discussed the use of an atypical antipsychotic in a patient with psychotic symptoms that had co-morbid PTSD.[30]

TREATMENT GUIDELINES AND SUMMARY

The American Psychiatric Association last released guidelines for the treatment of PTSD in 2004. Atypical antipsychotics including risperidone, olanzapine, and quetiapine received a level III recommendation which means there was a lack of evidence supporting their use but they may be considered on the basis of individual circumstances.

Veteran Affairs/Department of Defense guidelines were updated more recently in 2010. These guidelines provide an extensive review of the treatment of PTSD and lengthy review of evidence for and against specific pharmacotherapy. SSRIs and SNRIs have a strong recommendation as first line therapy. Sertraline, fluoxetine, paroxetine, and venlafaxine all have well controlled trials demonstrating their benefits in numerous patients. Second line options include mirtazapine, prazosin (for nightmares), TCAs, nefazodone, and MAOIs. These agents have all demonstrated some benefit in the treatment of PTSD. Veteran Affairs/Department of Defense guidelines state there is still insufficient evidence to support the use of atypical antipsychotics as monotherapy or adjunctive therapy when treating PTSD. With the results of the Veterans Affairs Cooperative Study, guidelines have been updated and recommend against the use of risperidone as augmentation therapy in patients with PTSD.[16]

Certain patients may benefit from therapy with an atypical antipsychotic, particularly for those with hyper-arousal or re-experiencing symptom clusters. However, it is important to keep in mind that this has only been found for olanzapine, quetiapine, and aripiprazole, and often times the data were conflicting, not very robust, and studies had limited sample sizes and narrow demographics. It is also important to provide proper patient education and weigh the risks versus benefits of therapy with an atypical antipsychotic as metabolic side effects are well documented in this class. Further large scale randomized controlled trials are needed to fully ascertain the true benefit of atypical antipsychotics and their role in the treatment of PTSD.

Table 1. Summary or trials using atypical antipsychotics in post traumatic stress disorder (ptsd): Risperidone

Study	Study design	Population	Intervention	Primary Outcome
Monnelly et al. 2003	6 week double blind RCT	16 combat veterans with PTSD	Risperidone: up to 2 mg daily vs. Placebo	Change from baseline OAS-M total score Risperidone: -17.0 Placebo: -9.5 P = 0.79
Hamner et al. 2003	5 week double blind RCT	40 combat veterans with PTSD and comorbid psychotic features	Risperidone: up to 6 mg daily vs. Placebo	Change from baseline PANSS total score Risperidone: -10 Placebo: -2.3 P ≤ 0.0488
Reich et al. 2004	8 week double blind RCT	21 women with PTSD due to childhood abuse	Risperidone: up to 8 mg daily vs. Placebo	Change from baseline CAPS-2 score Risperidone: -29.6 (34.5 SD) Placebo: -18.6 (12.3 SD) P < 0.001
Bartzokis et al. 2004	16 week double blind RCT	65 male veterans with chronic PTSD	Risperidone: fixed dose titrated to 3 mg daily vs. Placebo	Change from baseline CAPS total score Risperidone: -14.3 (16.7 SD) Placebo: -4.6 (13.2 SD) P < 0.001
Rothbaum et al. 2008	16 week RCT with 2 phases, each 8 weeks. Phase 2 was double blind	25 patients with PTSD without remission on sertraline entered phase 2 risperidone augmentation	Phase 2 Risperidone: 0.5-3 mg daily vs. Placebo	Change from CAPS total score from beginning of phase 2 to end of study Risperidone: -23.1 (12.9 SD) Placebo: -23.5 (19.6 SD) P=0.8
Krystal et al. 2011	6 month double blind RCT	267 patients randomized. Treatment resistant military related PTSD	Risperidone: up to 4 mg daily vs. Placebo	Change from baseline CAPS total score Risperidone: –16.3 (–19.7 to –12.9; 95% CI) Placebo: –12.5 (–15.7 to–9.4; 95% CI) Mean difference P=0.11

Study	Study design	Population	Intervention	Primary Outcome
Kozarić-Kovacić et al. 2005	6 week open label inpatient trial	27 male war veterans with psychotic PTSD	Risperidone: 2-4 mg daily (monotherapy)	Change from baseline PANNS total score Baseline: 135.5 (9.1 SD) 6 weeks: 51.9 (3.8 SD) P < 0.05
Padala et al. 2006	12 week double blind RCT	20 women with PTSD due to domestic violence or sexual assault	Risperidone: flexible dose (monotherapy) vs. Placebo	Change from baseline TOP-8 total score: Only a graph representation of data is provided in the study

RCT: Randomized controlled trial
OAS-M: Overt Aggression Scale Modified for Outpatients
PANNS: Positive and Negative Symptoms Scale
CAPS-2: Clinician administered PTSD scale- 1 week version
CAPS: Clinician Administered PTSD Scale
TOP-8: Treatment Outcomes Post-traumatic Stress Disorder Scale-8

Table 2. Summary or trials using atypical antipsychotics in post traumatic stress disorder (ptsd): Olanzapine

Study	Study Design	Population	Intervention	Primary Outcome
Butterfield et al. 2001	10-week RCT	15 total: 1 male and 14 female with civilian (5/15) or military trauma (10/15)	Flexible dose Olanzapine: up to 20 mg daily vs. Placebo	Change from baseline in SIP and SPRINT scales Baseline SIP Olanzapine: 39.7 (9.7 SD) Placebo: 45.9 (8.2 SD) Week 10 SIP Olanzapine: 19.2 (8.7 SD) Placebo: 17.0 (17.5 SD) Baseline SPRINT Olanzapine: 31.5 (5.7 SD) Placebo: 34.8 (2.1 SD) Week 10 SPRINT Olanzapine: 17.9 (7.8 SD) Placebo: 20.5 (11.1 SD) Difference were deemed non significant
Petty et al. 2001	8-week open-label trial	46 male veterans with chronic combat-related PTSD	Flexible dose olanzapine: up to 20 mg daily	Change from baseline of CAPS score Olanzapine: -85.17 Placebo: - 59.78 P<0.001
Stein, Kline, and Matloff 2002	12-week double blind RCT	19 male veterans with chronic combat-related PTSD who did not respond to SSRI therapy at maximally tolerated dose	Stable dose of SSRI at initiation Olanzapine: 10mg daily vs. placebo	Reduction in CAPS total score from baseline olanzapine: -14.80 Placebo: -2.67 P<0.05
Carey et al. 2012	8-week double blind RCT	34 males and females with civilian trauma related PTSD	Flexible dose olanzapine up to 15mg daily vs. placebo	Reduction in CAPS total score from baseline Olanzapine: -35.86 (19.85 SD) Placebo -19.29 (28.77 SD) P=0.018

RCT: Randomized controlled trial
SIP: Structured Interview for PTSD
SPRINT: Short PTSD Rating Interview
CAPS: Clinician Administered PTSD Scale
CGI-I: Clinical Global Impressions – Improvement Scale

Table 3. Summary or trials using atypical antipsychotics in post traumatic stress disorder (ptsd): Quetiapine

Study	Study design	Population	Intervention	Primary Outcome
Hamner et al. 2003	6 week open label trial with no control	20 patients with PTSD mostly combat related	Quetiapine: 25-300 mg daily	Change from baseline CAPS total score Baseline: 89.8 ± 15.7 Week 6: 67.5 ± 21.0 P<0.0005
Robert et al. 2005	Analysis of sleep data from Hamner et al. 2003	20 patients with PTSD mostly combat related	Quetiapine: 25-300 mg daily	Change from baseline PSQI score Baseline: 15.8 (2.72 SD) Week 6: 7.89 (5.15 SD) P<0.001
Ahearn et al. 2008	8 week open label trial with no control	15 patients with PTSD both combat and non-combat related	Quetiapine: 100-400 mg daily	Change from baseline CAPS total score Baseline: 80 (21) Week 8: 46 (31) P ≤ 0.0010
Byers et al. 2010	Historical prospective cohort trial	237 Veterans with PTSD	Quetiapine vs. Prazosin	Short term effectiveness by chart documentation Prazosin 61.3% Quetiapine 61.7% P = 0.54 Long term effectiveness by treatment continuation Prazosin 48.4% Quetiapine 24% P < 0.001

PSQI: Pittsburgh Sleep Quality Index
CAPS: Clinician Administered PTSD Scale

Table 4. Summary or trials using atypical antipsychotics in post traumatic stress disorder (ptsd): Aripiprazole

Study	Study Design	Population	Intervention	Primary Outcome
Lambert 2005	Case Series	5 independent case series, males and 1 female with PTSD in veterans returning from the Global War on Terrorism	Flexible dose aripiprazole up to max dose of 30mg daily + sertraline and/or CBT	Improvement of symptoms in 4 of 5 cases
Mello et al. 2008	16-week open-label trial	8 men and 24 women with PTSD from civilian trauma in Sao Paulo Brazil	Flexible dose aripiprazole up to max dose of 15mg daily	A 30% improvement in CAPS mean scores from baseline (82.7±23.1) to endpoint (51.4±31.4); 38% reduction achieved p=0.001
Richardson et al. 2011	12-week retrospective chart review of open-label aripiprazole as an adjunct therapy	26 men, 1 woman with military related PTSD	All patients taking an antidepressant prior to addition of flexible dose aripiprazole. Max dose of 30mg daily	Improvement in BDI and PCL-M scores baseline: PCL-M: 56.11 BDI : 30.44 week 12: PCL-M: 46.85; p<0.0001 BDI: 20.67 p<0.0001
Youssef et al. 2012	12-week open label monotherapy trial	5 men, 5 women veterans with PTSD	Flexible dose aripiprazole from 5-30mg daily	Change in total CAPS score from baseline to week 12 was statistically significant p<0.01

CBT – Cognitive Behavioral Therapy
PCL-M – PTSD Checklist Military Version
BDI – Beck's Depression Inventory

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