PSYCHIATRY ALERTS NOS

Volume XI / June 2019 / Number 6 www.alertpubs.com

Comparative Effectiveness of PTSD Treatments

A network meta-analysis of all available direct comparisons suggests that psychotherapy, pharmacotherapy, and their combination have similar short-term outcomes in PTSD.[1] However, long-term outcomes appear to be inferior with pharmacotherapy.

Background: Recent systematic reviews and meta-analyses comparing PTSD treatments have been largely based on indirect evidence, comparing either major category of treatment—psychological or pharmacological—with control conditions. Results suggested that psychotherapeutic options were more effective than medication. However, when comparing such different treatment approaches, this type of indirect evidence is considered highly problematic.

Methods: For the present network meta-analysis, a comprehensive literature search identified only randomized trials that directly compared psychotherapeutic and pharmacological treatments in adults with PTSD. If the studies also included a wait-list or placebo control, that condition was also included in the analysis. The primary outcome was PTSD symptom severity, measured using a validated scale. Outcomes were assessed immediately after treatment and at the longest available follow-up.

Results: The analysis was based on 12 published studies including 23 direct comparisons in a total of 922 participants. Of these, 6 investigated long-term outcomes. Most of the studies were conducted in patient groups with mixed trauma; 1 study each evaluated military veterans, survivors of a terror attack, victims of serious injury and sexual or nonsexual violence, and survivors of motor vehicle collisions. Medications were generally SSRIs, used for 8–24 weeks. Psychological treatments included cognitive-behavioral therapy, eye movement desensitization and reprocessing (EMDR), prolonged exposure therapy, and the Seeking Safety intervention.

Short-term results for psychotherapy, pharmacotherapy, and the combination were similar: the standard mean difference* (SMD) for all comparisons between treatment categories was below the prespecified threshold for a small difference. For long-term findings, psychotherapy was significantly superior to pharmacotherapy (SMD, 0.83). Combined treatment was also superior

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5641) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Subscription $105 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157.00 institutional. Subscribers may enroll in the 12-month CME program for $83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

to medication (SMD, 0.96). Psychotherapy and combined therapy were generally equivalent. In terms of acceptability, psychotherapeutic treatments had slightly lower dropout rates than the other types of treatment, but differences were not statistically significant.

Discussion: Despite the relatively small number of identified studies, these results suggest psychotherapeutic and pharmacological therapies have similar short-term efficacy. However, the analysis of longer-term outcomes, suggests inferiority of pharmacological monotherapies, confirming the common recommendation to try a psychotherapeutic option as first-line treatment.

Editorial.[2] These results should be interpreted cautiously because the analysis has many limitations. Due to the small amount of available evidence, studies with vastly different objectives were grouped (i.e., proof-of-concept, efficacy, and comparative effectiveness studies). In addition, there was heterogeneity among treatments included within categories; for example, the highly recommended trauma-focused therapies were grouped with other types, and medication trials included augmentation with atypical antipsychotics and one-time administration of experimental agents. Sample sizes were as small as 12, and even larger trials, with a few hundred participants, were not large enough to identify factors that could predict outcomes in different patients. Currently, patient preference often determines the initial choice between medication and psychotherapy. In spite of this research, clinicians are still left not knowing what to do when the initial treatment fails. The primary contribution of this meta-analysis may be that it points out just how few trials have been conducted in patients with PTSD and highlights the inadequacy of available evidence to answer important clinical questions.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, information on the study's funding was not included.

[1]Merz J, Schwarzer G, Gerger H: Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. *JAMA Psychiatry* 2019 doi 10.1001/jamapsychiatry.2019.0951. From the University of Basel, Switzerland; and the University of Freiburg, Germany. **Source of funding not stated. Two study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

[2]Stein M, Norman S: When does meta-analysis of a network not work? Fishing for answers [editorial]. *JAMA Psychiatry* 2019 doi 10.1001/jamapsychiatry.2019.0902. From the University of California San Diego, La Jolla, CA; and other institutions. **One author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

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Effectiveness of Suicide Prevention

Suicide prevention interventions are effective at preventing both suicide attempts and completed suicides, with medium effect sizes, according to the results of a meta-analysis. Efficacy differed according to the setting of the intervention, and multilevel interventions had a synergistic effect.

Methods: A comprehensive literature search identified comparative studies, with randomized or nonrandomized designs, published after 2010 that had suicide attempts or suicides as a primary outcome. Suicide prevention strategies included community approaches, psychotherapy, pharmacotherapy, and multilevel approaches. Treatment settings included outpatient mental health clinics, emergency departments, community facilities, and general hospital psychiatric wards. The primary aims of the meta-analysis were to estimate the effects of interventions on prevention of suicides and suicide attempts, to determine if treatment setting affected outcomes, and to assess whether multilevel interventions had additive effects.

Results: The search identified 16 studies with >250,000 participants: 14 that offered a single-level intervention and 1 each offering 2 or 3 levels. Thirteen studies were cluster randomized

trials, 2 used a before-and-after design, and 1 was a case-control study. The efficacy outcome was completed suicide in 2 studies, suicide attempts in 7, and both types of suicidal behavior in 7. The studies varied widely in methodologic quality, but there was no evidence of publication bias. One large study was excluded from the meta-analysis because of methodologic differences that made pooling the results impossible.

In total, the studies reported 62 suicides and 1006 suicide attempts in a combined sample of >29,000 patients. Overall, the meta-analysis found prevention efforts significantly reduced the combined endpoint of completed suicide and suicide attempts (effect size [ES],* 0.495; p<0.001). Effects on completed suicide were somewhat larger than those for suicide attempt (ES, 0.535 and 0.449, respectively). Treatment setting also affected outcomes. When completed suicides and attempts were evaluated separately, outpatient specialty mental health clinics were the only setting in which the effect on suicide attempts was large (ES, 0.75). For completed suicides, interventions administered on a general hospital psychiatric ward (ES, 1.08) and community-level interventions (ES, 0.832) had the largest effects, followed by emergency-room interventions (ES, 0.289). Outpatient specialty clinic interventions had virtually no effect on completed suicides. Although only 2 interventions were multilevel, the meta-analysis showed a statistically significant synergistic effect (p=0.032), with effect sizes of 0.3 for single-level interventions, 0.5 for 2 levels, and 0.8 for 3 levels.

Discussion: These results suggest that suicide prevention interventions are effective, with a larger effect on completed than attempted suicides. A possible explanation is that suicide attempters and completers may differ in population characteristics and in the lethality of methods chosen. The 2 groups also differ in the relative effects of different intervention settings.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Hofstra E, van Nieuwenhuizen C, Bakker M, Ozgul D, et al: Effectiveness of suicide prevention interventions: a systematic review and meta-analysis. *General Hospital Psychiatry* 2019; doi 10.1016/j.genhosppsych.2019.04.011. From GGz Breburg, the Netherlands; and other institutions. **Funded by the Netherlands Organisation for Health Research and Development. The authors declared no competing interests.**

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Dynamic Interpersonal Therapy for Depression

A pilot study found dynamic interpersonal therapy (DIT), a form of short-term psychodynamic therapy, to be effective and feasible in patients with moderate to severe depression. DIT is unique among psychodynamic therapies in providing a treatment manual and curriculum that can be used by clinicians without extensive training in psychodynamic therapy, potentially extending the availability of this approach.

Methods: The study was conducted within the British Improving Access to Psychological Therapies (IAPT) program, which implements evidence-based psychological therapies for common mental disorders in the community. The IAPT's stepped-care scheme for depression offers a low-intensity treatment of guided self-help for patients with less severe depression and low suicide risk, and high-intensity treatment—typically cognitive-behavioral therapy—for more severe depression. In the present study, DIT was compared with both low-intensity treatment (LIT) and CBT in adults with a DSM-IV major depressive episode of at least moderate severity (i.e., Hamilton Rating Scale for Depression [HAM-D] score >14). DIT is based on attachment and mentalization theory and focuses on the patient's core, repetitive pattern of relating, called the interpersonal affective focus, and how it gives rise to depressive symptoms. Patients were randomly assigned to receive DIT, delivered in 16 weekly 1-hour sessions, or 1 of the control treatment (i.e., LIT or CBT) delivered over a comparable

time span and with similar intensity. The primary study outcome, assessed by blinded raters, was change from baseline to 6 months in HAM-D score.

Results: The study sample comprised 147 patients with an average HAM-D score of about 19; 73 received DIT, 54 the low-intensity intervention, and 20 CBT. Five of the patients randomized to DIT did not begin therapy, and 13 terminated the intervention early. All patients were included in the intent-to treat outcome analysis.

Patients in the DIT group demonstrated linear improvement in HAM-D scores over time, in contrast to the low-intensity group, whose improvement plateaued between the middle and end of treatment. At the 6-month post-treatment evaluation, mean HAM-D scores were 10 in the DIT group, compared with 15 in the low-intensity treatment group (p=0.004; effect size,*0.70) and 13 in the CBT group (p=ns). Rates of study-defined clinically significant improvement were 51% with DIT, 20% with CBT, and 9% with low-intensity treatment. Few patients showed clinical deterioration. Follow-up at 12 months from the start of treatment showed that gains in the DIT group were maintained.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Fonagy P, Lemma A, Target M, O'Keefe S, et al: Dynamic interpersonal therapy for moderate to severe depression: a pilot randomized controlled and feasibility trial. *Psychological Medicine* 2019; doi 10.1017/S0033291719000928. From University College London, U.K.; and other institutions. **Funded by the National Institute for Health Research. Four of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Renin-Angiotensin Modulation in Schizophrenia

Evidence is accumulating that the central renin-angiotensin system (RAS) is involved in the pathophysiology of neuropsychiatric diseases including schizophrenia. The brain has an intrinsic RAS system that includes all precursors and enzymes needed for the formation of biologically active forms of angiotensin, as well as all major angiotensin receptor types. The central RAS has a broad-spectrum role, including neuroprotection, memory consolidation, and other more basic bodily processes. The RAS may influence outcomes in schizophrenia via its effects on inflammation, glutamate, dopamine, GABA, and peroxisome proliferator-activated receptor (PPAR)-γ.

Inflammation. Schizophrenia symptoms are related to disruption of inflammatory and immunological processes. The potential role of antiinflammatory agents in the treatment of schizophrenia has been investigated, with mixed results. It remains unclear whether immune dysfunction is a direct result of a pathologic state in the central immune system or is secondary to other clinical and systemic factors associated with schizophrenia. Brain imaging and autopsy studies have been inconclusive. The proinflammatory properties of angiotensin II have been demonstrated. In patients with medical illnesses, angiotensin receptor blockers (ARBs), which modulate the RAS, reduce angiotensin-mediated inflammation and oxidative stress. It is therefore possible that these agents could mediate clinical symptoms of schizophrenia via these mechanisms.

Glutamate. Abnormal glutamate levels have been demonstrated in patients with first-episode and treatment-resistant schizophrenia. Abnormal glutamatergic signaling secondary to excessive stimulation of non-NMDA glutamate receptors may result in neuronal injury. ARBs may prevent glutamate-mediated cell injury by reducing oxidative stress and by restoring neurotransmitter homeostasis.

Dopamine. In schizophrenia, dopamine activity is elevated in some brain regions and reduced in others. Some brain structures have both dopamine and angiotensin receptors. Decreased

dopamine activity may induce compensatory upregulation of local RAS function, possibly leading to oxidative stress and neurotoxicity. Inhibition of the brain RAS might protect against dopaminergic deficit, which could lead to clinical improvement, especially in the domains of negative symptoms and cognition.

GABA. Altered GABA transmission is suspected to be involved in the cognitive disturbances of schizophrenia. Restoration of GABA expression via RAS modulation could have favorable effects on cognitive impairment. In addition, ARBs have both antiinflammatory and immune activity that has been attributed at least in part to restored GABA expression. Increasing GABA levels via RAS inhibition could mediate the antiinflammatory and immune processes in schizophrenia.

PPAR-γ. Activation of the nuclear transcription factor PPAR-γ can produce beneficial effects on lipid and glucose metabolism, and PPAR-γ agonists are used to treat insulin resistance, diabetes mellitus, and metabolic syndrome. In addition to these systemic effects, PPAR-γ appears to have numerous protective effects in the brain, and its activity may be reduced in schizophrenia. Although there is no proof of a causal relationship between PPAR-γ alterations and schizophrenia, some RAS modulators act as PPAR-γ agonists, suggesting they may have potential for use in schizophrenia treatment.

Although there is currently no consensus on the exact mechanisms by which the central RAS may be involved in the pathophysiology of schizophrenia, multiple possibilities are biologically plausible. Potentially, drugs that affect the RAS system may be effective in schizophrenia by optimizing levels of glutamate, dopamine, and GABA, and possibly PPAR-γ.

Oh S, Fan X: The possible role of the angiotensin system in the pathophysiology of schizophrenia: implications for pharmacotherapy. *CNS Drugs* 2019;33:539–547. doi 10.1007/s40263-019-00632-4. From the University of Massachusetts Medical School; and UMass Memorial Medical Center, Worcester. **This review was conducted without funding. One author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Psychological Intervention for Prolonged Grief

According to a meta-analysis of controlled trials, psychological interventions for grief in adults have small but significant positive and lasting effects on grief symptoms. Treatments may have larger effects if they are offered to individuals who are ≥6 months post-loss and who have more severe baseline symptoms.

Methods: A comprehensive literature review identified randomized controlled trials of psychological therapy conducted in adults, aged ≥18 years at the time of loss, and having experienced the death of a living person (i.e., not a pet or a stillbirth). Included studies were required to use a quantitative measure of prolonged grief symptoms and to evaluate a cognitive-behavioral, emotional/supportive, or psychoeducational intervention provided by a health professional. The primary outcome of the analysis was the change from baseline in grief symptoms, measured with a standardized instrument, with priority given to the Inventory of complicated Grief–Revised and the Prolonged Grief-13 instrument. Secondary outcomes included depressive symptoms, posttraumatic stress symptoms, and distress.

Results: The meta-analysis included 31 studies, with a combined sample size of 4760 adults (mean age, 50 years; 73% women). Most studies (n=25) included follow-up observations after treatment completion (mean follow-up duration, 10 months). The mean attrition rate was 17% at the end of treatment and 26% at follow-up. The majority of studies (88%) used a grief-specific intervention such as support groups, expressive writing, cognitive-behavioral therapy, behavioral activation therapy, internet-based treatments, psychoeducation, or family interventions. Control groups received active but nonspecific interventions such as attention or active

listening and passive conditions such as wait-listing. The treatments were initiated an average of 36 months post-loss (range, 2–123 months), and 22 studies were limited to participants with high baseline symptoms. The men number of sessions across interventions was 10 (range, 1–20).

In the pooled analysis, the effect of for psychological interventions on grief symptoms was positive, but small at the post-intervention evaluation (effect size [ES],* 0.41; p<0.001) and at follow-up (ES, 0.45; p<0.001). Effects of a similar magnitude were observed for depressive symptoms, posttraumatic stress symptoms, and distress (p≤0.001 for all). Treatments delivered in an individual format had significantly larger effects post-intervention than those delivered in a group format (ES, 0.49; p<0.001), as did studies requiring participants to have high baseline symptoms (ES, 0.40; p=0.002), and studies requiring participants to be ≥6 months post-loss (ES, 0.58; p<0.001).

Discussion: A medium effect size (≥0.5) has been suggested to correspond to a clinically important change in self-reported outcomes, and while the overall effects found in this study were somewhat smaller, improvement appears to be more robust in persons who are ≥6 months post-loss and who receive individual therapy.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Johannsen M, Damholdt M, Zachariae R, Lundorff M, et al: Psychological interventions for grief in adults: a systematic review and meta-analysis of randomized controlled trials. *Journal of Affective Disorders* 2019;253:69-86. doi 10.1016/j.jad.2019.04.065. From Aarhus University, Denmark. T**his study was conducted with no external funding. The authors declared no competing interests.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Standardized Mean Difference: The difference between two normalized means. Used for comparison of data obtained using different scales, a value of 0–0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and >0.8 a large effect.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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