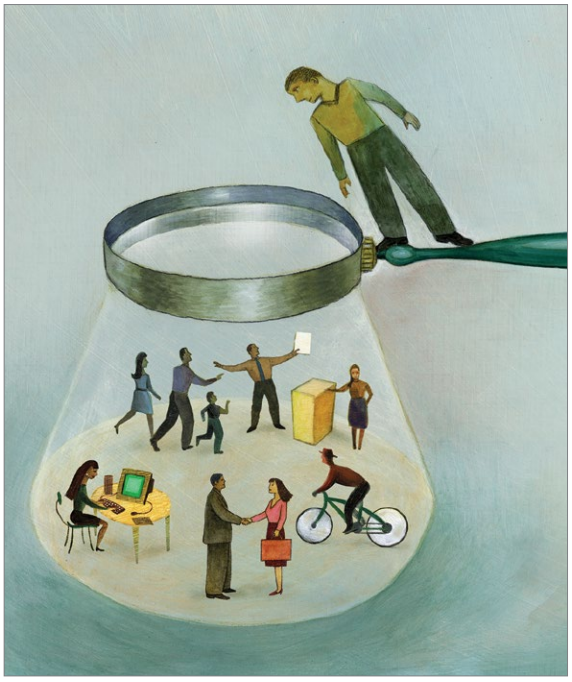
Current PSYCHIATRY

SECOND OF 2 PARTS

Top research findings of 2018-2019 for clinical practice



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These studies may change how you treat schizophrenia, MDD, alcohol use disorder, more

In Part 1 of this article, published in Current Psychiatry January 2020,[1] I discussed how medical knowledge is growing faster than ever, and the challenge to keep up with the ever-growing body of information is greater than ever. I described a 3-step methodology I used to sort and evaluate published research that was ready for clinical application. This led me to select 12 top articles published between July 1, 2018 and June 30, 2019, chosen based on their clinical relevance/applicability. In Part 1 I discussed 6 of these 12 studies. In Part 2, I present brief descriptions of the remaining 6 papers chosen by this methodology. These studies are summarized in the ***Table***[2-7] (***page 23***). The order in which they appear in this article is arbitrary.

1. Han LKM, Aghajani M, Clark SL, et al. Epigenetic aging in major depressive disorder. Am J Psychiatry. 2018;175(8):774-782.

In light of the association of major depressive disorder (MDD) with an increased risk of aging-related diseases, Han et al[2] examined whether MDD was associated with higher epigenetic aging in blood as measured by DNA methylation patterns. They also studied whether clinical characteristics of MDD had a further impact on these patterns, and whether the findings replicated in brain tissue. Many differentially methylated regions of our DNA tend to change as we age. Han et al[2] used these age-sensitive differentially methylated regions to estimate chronological age,

Disclosure
The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

Table

Top psychiatric research findings of 2018-2019: Part 2

Study	Design	Outcomes
Han et al[2] (2018)	DNA methylation age was estimated using all methylation sites in the blood of 811 patients with MDD and 319 control participants with no lifetime psychiatric disorders	Compared with control participants, significantly higher epigenetic aging was observed in patients with MDD. In patients with MDD, epigenetic aging was significantly associated with childhood trauma
Wu et al[3] (2019)	Network meta-analysis of studies that investigated pharmacotherapy for the treatment (20 RCTs with 1,435 participants) or prevention (38 RCTs with 8,168 participants) of delirium	Compared with placebo/control, haloperidol plus lorazepam resulted in the best response rate for delirium treatment. Patients who received ramelteon, olanzapine, risperidone, or dexmedetomidine had significantly lower delirium occurrence rates than those receiving placebo/control
Simpson et al[4] (2018)	Double-blind, 12-week trial in which 92 patients with alcohol use disorder were randomly assigned to receive prazosin or placebo	Compared with those who received placebo, patients who received prazosin reported fewer heavy drinking days and fewer drinks per week
Meltzer-Brody et al[5] (2018)	Two double-blind trials in which women with postpartum depression were randomly assigned to receive an IV infusion of brexanolone or placebo for 60 hours	Compared with placebo, brexanolone resulted in a significant, clinically meaningful reduction in HAM-D total score at 60 hours
Tiihonen et al[6] (2019)	Analysis of data from 62,250 patients with schizophrenia who were treated with 29 different antipsychotic monotherapy or polypharmacy regimens. Rehospitalization was used as a marker for relapse	Clozapine plus aripiprazole was associated with the lowest risk of rehospitalization, particularly among patients experiencing first-episode schizophrenia. Compared with any monotherapy, any antipsychotic polypharmacy was associated with a lower risk of rehospitalization
Stroup et al[7] (2019)	Analysis of US Medicaid data that included 81,921 patients with schizophrenia stably treated with a single antipsychotic who started adjunctive treatment with an antidepressant, benzodiazepine, mood stabilizer, or another antipsychotic	Compared with initiating another antipsychotic, initiating an antidepressant was associated with a lower risk of rehospitalization, and initiating a benzodiazepine was associated with a higher risk. Initiating a mood stabilizer was not significantly different from initiating another antipsychotic

HAM-D: Hamilton Depression Rating Scale; MDD: major depressive disorder; RCTs: randomized controlled trials

using DNA extracted from various tissues, including blood and brain.

Study design

- As a part of the Netherlands Study of Depression and Anxiety (NESDA), this study included 811 patients with MDD and 319 control participants with no lifetime psychiatric disorders and low depressive symptoms (Inventory of Depressive Symptomatology score <14).
- Diagnosis of MDD and clinical characteristics were assessed by questionnaires and psychiatric interviews. Childhood trauma was assessed using the NEMESIS childhood trauma interview, which included a structured inventory of trauma exposure during childhood.
- DNA methylation age was estimated using all methylation sites in the blood of 811 patients with MDD and 319 control participants. The residuals of the DNA methylation age estimates regressed on chronological age were calculated to indicate epigenetic aging.
- Analyses were adjusted for sociodemographic characteristics, lifestyle, and health status.

continued

Clinical Point

Significantly higher epigenetic aging was observed in patients with MDD compared with control participants

Top research of 2018-2019

Clinical Point

Haloperidol plus lorazepam produced the best response rate for treating delirium

• Postmortem brain samples of 74 patients with MDD and 64 control participants were used for replication.

Outcomes

• Significantly higher epigenetic aging was observed in patients with MDD compared with control participants (Cohen's *d* = 0.18), which suggests that patients with MDD are biologically older than their corresponding chronological age. There was a significant dose effect with increasing symptom severity in the overall sample.

• In the MDD group, epigenetic aging was positively and significantly associated with childhood trauma.

• The case-control difference was replicated in an independent analysis of postmortem brain samples.

Conclusion

• These findings suggest that patients with MDD and people with a history of childhood trauma may biologically age relatively faster than those without MDD or childhood trauma. These findings may represent a biomarker of aging and might help identify patients who may benefit from early and intensive interventions to reduce the physical comorbidities of MDD.

• This study raises the possibility that MDD may be causally related to epigenetic age acceleration. However, it only points out the associations; there are other possible explanations for this correlation, including the possibility that a shared risk factor accounts for the observed association.

2. Wu YC, Tseng PT, Tu YK, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. JAMA Psychiatry. 2019; 76(5):526-535.

Delirium is common and often goes underdiagnosed. It is particularly prevalent among hospitalized geriatric patients. Several medications have been suggested to have a role in treating or preventing delirium. However, it remains uncertain which medications provide the best response rate, the lowest rate of delirium occurrence, and the best tolerability. In an attempt to find answers to these questions, Wu et al[3] reviewed studies that evaluated the use of various medications used for delirium.

Study design

• Researchers conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) that investigated various pharmacologic agents used to treat or prevent delirium.

• Fifty-eight RCTs were included in the analyses. Of these, 20 RCTs with a total of 1,435 participants compared the outcomes of treatments of delirium, and 38 RCTs with a total of 8,168 participants examined prevention.

• A network meta-analysis was performed to determine if an agent or combinations of agents were superior to placebo or widely used medications.

Outcomes

• Haloperidol plus lorazepam provided the best response rate for treating delirium compared with placebo/control.

• For delirium prevention, patients who received ramelteon, olanzapine, risperidone, or dexmedetomidine had significantly lower delirium occurrence rates than those receiving placebo/control.

• None of the pharmacologic treatments were significantly associated with a higher risk of all-cause mortality compared with placebo/control.

Conclusion

• Haloperidol plus lorazepam might be the best treatment and ramelteon the best preventive medicine for delirium. None of the pharmacologic interventions for treatment or prophylaxis increased all-cause mortality.

• However, network meta-analyses involve extrapolating treatment comparisons that are not made directly. As Blazer[8] pointed out, both findings in this study (that haloperidol plus lorazepam is a unique intervention among the treatment trials and ramelteon is a unique intervention for prevention) seemed to be driven by 2 of the 58 studies that Wu et al[3] examined. Wu et al[3] also cautioned that both of

these interventions needed to be further researched for efficacy.

3. Simpson TL, Saxon AJ, Stappenbeck C, et al. Double-blind randomized clinical trial of prazosin for alcohol use disorder. Am J Psychiatry. 2018;175(12):1216-1224.

While some evidence suggests that elevated brain noradrenergic activity is involved in the initiation and maintenance of alcohol use disorder,[9] current medications used to treat alcohol use disorder do not target brain noradrenergic pathways. In an RCT, Simpson et al[4] tested prazosin, an alpha-1 adrenergic receptor antagonist, for the treatment of alcohol use disorder.

Study design

- In this 12-week double-blind study, 92 participants with alcohol use disorder were randomly assigned to receive prazosin or placebo. Individuals with posttraumatic stress disorder were excluded.
- Prazosin was titrated to a target dosing schedule of 4 mg in the morning, 4 mg in the afternoon, and 8 mg at bedtime by the end of Week 2. The behavioral platform was medical management. Participants provided daily data on their alcohol consumption.
- Generalized linear mixed-effects models were used to examine the impact of prazosin compared with placebo on number of drinks per week, number of drinking days per week, and number of heavy drinking days per week.

Outcomes

- Among the 80 participants who completed the titration period and were included in the primary analyses, prazosin was associated with self-reported fewer heavy drinking days, and fewer drinks per week (–8 vs –1.5 with placebo). Drinking days per week and craving showed no group differences.
- The rate of drinking and the probability of heavy drinking showed a greater decrease over time for participants receiving prazosin compared with those receiving placebo.

Conclusion

- These findings of moderate reductions in heavy drinking days and drinks per week with prazosin suggest that prazosin may be a promising harm-reduction treatment for alcohol use disorder.

4. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet. 2018;392(10152):1058-1070.

Postpartum depression is among the most common complications of childbirth. It can result in considerable suffering for mothers, children, and families. Gamma-aminobutyric acid (GABA) signaling has previously been reported to be involved in the pathophysiology of postpartum depression. Meltzer-Brody et al[5] conducted 2 double-blind, randomized, placebo-controlled, phase 3 trials comparing brexanolone with placebo in women with postpartum depression at 30 clinical research centers and specialized psychiatric units in the United States.

Study design

- Participants were women age 18 to 45, ≤6 months postpartum at screening, with postpartum depression as indicated by a qualifying 17-item Hamilton Depression Rating Scale (HAM-D) score of ≥26 for Study 1 or 20 to 25 for Study 2.
- Of the 375 women who were screened simultaneously across both studies, 138 were randomly assigned (1:1:1) to receive a single IV injection of brexanolone, 90 µg/kg per hour (BRX90) (n = 45), brexanolone, 60 µg/kg per hour (BRX60) (n = 47), or placebo (n = 46) for 60 hours in Study 1, and 108 were randomly assigned (1:1) to receive BRX90 (n = 54) or placebo (n = 54) for 60 hours in Study 2.
- The primary efficacy endpoint was change in total score on the HAM-D from baseline to 60 hours. Patients were followed until Day 30.

Outcomes

- In Study 1, at 60 hours, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19.5 points (standard

Clinical Point

Prazosin may be a promising harm-reduction treatment for alcohol use disorder

Top research of 2018-2019

Clinical Point

Brexanolone injection produced a significant reduction in HAM-D scores in women with postpartum depression

error [SE] 1.2) in the BRX60 group and 17.7 points (SE 1.2) in the BRX90 group, compared with 14.0 points (SE 1.1) in the placebo group.

- In Study 2, at 60 hours, the LS mean reduction in HAM-D total score from baseline was 14.6 points (SE 0.8) in the BRX90 group compared with 12.1 points (SE 0.8) for the placebo group.
- In Study 1, one patient in the BRX60 group had 2 serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In Study 2, one patient in the BRX90 group had 2 serious adverse events (altered state of consciousness and syncope), which were considered treatment-related.

Conclusion

- Administration of brexanolone injection for postpartum depression resulted in significant, clinically meaningful reductions in HAM-D total score at 60 hours compared with placebo, with a rapid onset of action and durable treatment response during the study period. These results suggest that brexanolone injection has the potential to improve treatment options for women with this disorder.

5. Tiihonen J, Taipale H, Mehtälä J, et al. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. JAMA Psychiatry. 2019;76(5):499-507.

In clinical practice, the use of multiple antipsychotic agents for the maintenance treatment of schizophrenia is common but generally not recommended. The effectiveness of antipsychotic polypharmacy in preventing relapse of schizophrenia has not been established, and whether specific antipsychotic combinations are superior to monotherapies for maintenance treatment of schizophrenia is unknown. Tiihonen et al[6] investigated the association of specific antipsychotic combinations with psychiatric rehospitalization, which was used as a marker for relapse.

Study design

- This study included 62,250 patients with schizophrenia, treated between January 1, 1996 and December 31, 2015, in a comprehensive, nationwide cohort in Finland. Overall, 31,257 individuals (50.2%) were men, and the median age was 45.6 (interquartile range, 34.6 to 57.9).
- Patients were receiving 29 different antipsychotic monotherapy or polypharmacy regimens.
- Researchers analyzed data from April 24 to June 15, 2018 using psychiatric rehospitalization as a marker for relapse. To minimize selection bias, rehospitalization risks were investigated using within-individual analyses.
- The main outcome was the hazard ratio (HR) for psychiatric rehospitalization during use of polypharmacy vs monotherapy by the same patient.

Outcomes

- Clozapine plus aripiprazole was associated with the lowest risk of psychiatric rehospitalization, with a difference of 14% (HR, .86; CI, .79 to .94) compared with clozapine monotherapy in the analysis that included all polypharmacy periods, and 18% (HR, .82; CI, .75 to .89) in the conservatively defined polypharmacy analysis that excluded periods <90 days.
- Among patients experiencing their first episode of schizophrenia, the differences between clozapine plus aripiprazole vs clozapine monotherapy were greater, with a difference of 22% in the analysis that included all polypharmacy periods, and 23% in the conservatively defined polypharmacy analysis.
- At the aggregate level, any antipsychotic polypharmacy was associated with a 7% to 13% lower risk of psychiatric rehospitalization compared with any monotherapy.
- Clozapine was the only monotherapy among the 10 best treatments.
- Results on all-cause and somatic hospitalization, mortality, and other sensitivity analyses were in line with the primary outcomes.

Conclusion

- This study suggests that certain types of antipsychotic polypharmacy may reduce the risk of rehospitalization in patients with schizophrenia. Current

treatment guidelines state that clinicians should prefer antipsychotic monotherapy and avoid polypharmacy. Tiihonen et al[6] raise the question whether current treatment guidelines should continue to discourage antipsychotic polypharmacy in the maintenance treatment of schizophrenia.

• Despite the large administrative databases and sophisticated statistical methods used in this study, this approach has important limitations. As Goff[10] points out, despite efforts to minimize bias, these results should be considered preliminary until confirmed by RCTs.

6. Stroup TS, Gerhard T, Crystal S, et al. Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. JAMA Psychiatry. 2019;76(5):508-515.

In routine clinical practice, patients with schizophrenia are often treated with combinations of antipsychotics and other psychotropic medications. However, there is little evidence about the comparative effectiveness of these adjunctive treatment strategies. Stroup et al[7] investigated the comparative real-world effectiveness of adjunctive psychotropic treatments for patients with schizophrenia.

Study design

• This comparative effectiveness study used US Medicaid data from January 1, 2001, to December 31, 2010. Data analysis was performed from January 1, 2017, to June 30, 2018.

Related Resources

- NEJM Journal Watch. www.jwatch.org.
- F1000 Prime. https://f1000.com/prime/home.
- BMJ Journals Evidence-Based Mental Health. https://ebmh.bmj.com.

Drug Brand Names

Aripiprazole • Abilify
Brexanolone • Zulresso
Clozapine • Clozaril
Dexmedetomidine • Precedex
Haloperidol • Haldol
Lorazepam • Ativan
Olanzapine • Zyprexa
Prazosin • Minipress
Ramelteon • Rozerem
Risperidone • Risperdal

• The study cohort included 81,921 adult outpatients diagnosed with schizophrenia with a mean age of 40.7 (range: 18 to 64), including 37,515 women (45.8%). All patients were stably treated with a single antipsychotic and then started on an adjunctive antidepressant (n = 31,117), benzodiazepine (n = 11,941), mood stabilizer (n = 12,849), or another antipsychotic (n = 26,014).

• Researchers used multinomial logistic regression models to estimate propensity scores to balance covariates across the 4 medication groups. Weighted Cox proportional hazards regression models were used to compare treatment outcomes during 365 days on an intention-to-treat basis.

• The main outcomes and measures included risk of hospitalization for a mental disorder (primary), emergency department (ED) visits for a mental disorder, and all-cause mortality.

Outcomes

• Compared with starting another antipsychotic, initiating use of an antidepressant

Clinical Point

Compared with any antipsychotic monotherapy, any antipsychotic polypharmacy reduced the risk of rehospitalization

Bottom Line

Significantly higher epigenetic aging has been observed in patients with major depressive disorder. Haloperidol plus lorazepam might be an effective treatment for delirium; and ramelteon may be effective for preventing delirium. Prazosin reduces heavy drinking in patients with alcohol use disorder. A 60-hour infusion of brexanolone can help alleviate postpartum depression. Clozapine plus aripiprazole reduces the risk of rehospitalization among patients with schizophrenia. Adding an antidepressant to an antipsychotic also can reduce the risk of rehospitalization among patients with schizophrenia.

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Clinical Point

Adding an antidepressant to an antipsychotic was associated with substantially reduced rates of hospitalization

was associated with a lower risk of psychiatric hospitalization, and initiating use of a benzodiazepine was associated with a higher risk. Initiating use of a mood stabilizer was not significantly different from initiating use of another antipsychotic.

- A similar pattern of associations was observed in psychiatric ED visits for initiating use of an antidepressant, benzodiazepine, or mood stabilizer.
- Initiating use of a mood stabilizer was associated with an increased risk of mortality.

Conclusion

- Compared with the addition of a second antipsychotic, adding an antidepressant was associated with substantially reduced rates of hospitalization, whereas adding a benzodiazepine was associated with a modest increase in the risk of hospitalization. While the addition of a mood stabilizer was not associated with a significant difference in the risk of hospitalization, it was associated with higher mortality.
- Despite the limitations associated with this study, the associations of benzodiazepines and mood stabilizers with poorer outcomes warrant clinical caution and further investigation.

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