Dear Colleagues,

We are excited to bring you a July/August edition of Psychiatric Practice Updates! Since the New England Journal of Medicine Journal Watch for Psychiatry went out of business in December 2020, Dr. Joel Yager has compiled monthly issues of Psychiatric Practice Updates, sharing his curated list of articles to inform your clinical practice. These compilations have been sent to psychiatrists across the world and the lifelong learning continuum. With his recent retirement, Dr. Yager has handed this project over to our newly created Psychiatric Practice Updates Committee - a group of faculty and trainees from David Geffen School of Medicine at UCLA and Harvard Medical School. We thank Dr. Yager for sharing his love of learning with all of us and inspiring us to continue this important work.

We will be conducting reviews of over 20 peer-reviewed journals each month with the goal of selecting articles that are interesting, impactful, and clinically relevant. Through our reviews, we may also highlight articles that advance our scientific understanding of mental illness or service delivery.

We have provided a list of articles that we selected from our July and August reviews, followed by the abstracts and pubmed links. Feel free to share and disseminate.

If you would like to receive the monthly Psychiatric Practice Updates email, please send an email with SUBSCRIBE in the subject to PsychiatricPracticeUpdates@gmail.com

Happy learning!

The Psychiatric Practice Updates Committee

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PSYCHIATRIC PRACTICE UPDATES – JULY/AUGUST

EFFECT OF NIGHTTIME BEDROOM LIGHT EXPOSURE ON MOOD EPISODE RELAPSES IN BIPOLAR DISORDER

Esaki Y, Obayashi K, Saeki K, Fujita K, Iwata N, Kitajima T. Effect of nighttime bedroom light exposure on mood episode relapses in bipolar disorder. Acta Psychiatr Scand. 2022 Jul;146(1):64-73. doi: 10.1111/acps.13422. Epub 2022 Mar 9. PMID: 35253206.

Objective: A previous cross-sectional study reported that nighttime light is associated with increased occurrence of manic symptoms in bipolar disorder; however, the longitudinal association between nighttime light and subsequent mood episode relapses remains unclear. We determined whether bedroom nighttime light was associated with mood episode relapses in patients with bipolar disorder.
Methods: This prospective cohort study included 172 outpatients with bipolar disorder who participated in an Association between the Pathology of Bipolar Disorder and Light Exposure in Daily Life (APPLE) cohort study. A portable photometer was used to measure illuminance in the bedroom from bedtime to rising time during 7 consecutive nights for baseline assessment. Then, the participants were assessed at a 2-year follow-up for mood episode relapses.
Results: Of the 172 participants, 157 (91%) completed the 2-year follow-up, and 39 (22%) experienced manic or hypomanic episodes (with or without mixed features), during that time. In the Cox proportional-hazards model, the hazard ratio (HR) for manic/hypomanic episode relapses was significantly higher when the average nighttime illuminance was ≥3 lux (n = 71) than when it was <3 lux (n = 101; HR, 2.54; 95% confidence interval (CI), 1.33-4.84). In the multivariable model adjusted for a propensity score in relation to nighttime light, the relationship remained significant (HR, 2.17; 95% CI, 1.04-4.52). The association between nighttime light and depressive episode relapses was not significantly different.

Conclusions: Keeping the bedroom dark at night may prevent hypomanic and manic episodes.

OPTIMAL DOSE OF ARIPIPRAZOLE FOR AUGMENTATION THERAPY OF ANTIDEPRESSANT-REFRACTORY DEPRESSION: PRELIMINARY FINDINGS BASED ON A SYSTEMATIC REVIEW AND DOSE-EFFECT META-ANALYSIS.

Furukawa Y, Hamza T, Cipriani A, Furukawa TA, Salanti G, Ostinelli EG. Optimal dose of aripiprazole for augmentation therapy of antidepressant-refractory depression: preliminary findings based on a systematic review and dose-effect meta-analysis. Br J Psychiatry. 2022 Aug;221(2):440-447. doi: 10.1192/bjp.2021.165. PMID: 35049482.

Background: Aripiprazole augmentation is proven effective for antidepressant-refractory depression, but its licensed dose range is wide and optimal dosage remains unclear.
Aims: To find the optimal dosage of aripiprazole augmentation.
Method: Multiple electronic databases were searched (from inception to 16 February 2021) to identify all assessor-masked randomised controlled trials evaluating aripiprazole augmentation therapy in adults (≥18 years old, both genders) with major depressive disorder showing inadequate response to at least one antidepressant treatment. A random-effects, one-stage dose-effect meta-analysis with restricted cubic splines was conducted. Outcomes were efficacy (treatment response: ≥50% reduction in depression severity), tolerability (drop-out due to adverse effects) and acceptability (drop-out for any reason) after 8 weeks of treatment (range 4-12 weeks).
Results: Ten studies met the inclusion criteria. All were individually randomised, placebo-controlled, multi-centre, parallel studies including 2625 participants in total. The maximum target dose-efficacy curve showed an increase up to doses between 2 mg (odds ratio OR = 1.46, 95% CI 1.15-1.85) and 5 mg (OR = 1.93, 95% CI 1.33-2.81), and then a non-increasing trend through the higher licensed doses up to 20 mg (OR = 1.90, 95% CI 1.52-2.37). Tolerability showed a similar trend with greater uncertainty. Acceptability showed no significant difference through the examined dose range. Certainty of evidence was low to moderate.
Conclusions: Low-dose aripiprazole as augmentation treatment might achieve the optimal balance between efficacy, tolerability and acceptability in the acute treatment of antidepressant-refractory depression. However, the small number of included studies and the overall moderate to high risk of bias seriously compromise the reliability of the results. Further research is required to investigate the benefits of low versus high dose.

ASSOCIATION BETWEEN DEPRESSION AND EPIGENETIC AGE ACCELERATION: A CO-TWIN CONTROL STUDY.

Liu C, Wang Z, Hui Q, Goldberg J, Smith NL, Shah AJ, Murrah N, Shallenberger L, Diggers E, Bremner JD, Sun YV, Vaccarino V. Association between depression and epigenetic age

acceleration: A co-twin control study. Depress Anxiety. 2022 Jun 27. doi: 10.1002/da.23279. Epub ahead of print. PMID: 35758529.

Introduction: Prior studies have shown inconsistent findings of an association between depression and epigenetic aging. DNA methylation (DNAm) age acceleration can measure biological aging. We adopted a robust co-twin control study design to examine whether depression is associated with DNAm age acceleration after accounting for the potential confounding influences of genetics and family environment.
Methods: We analyzed data on a sub-cohort of the Vietnam Era Twin Registry. A total of 291 twins participated at baseline and 177 at follow-up visit after a mean of 11.7 years, with 111 participants having DNA samples for both time points. Depression was measured using the Beck Depression Inventory II (BDI-II). Six measures of DNAm age acceleration were computed at each time point, including Horvath's DNAm age acceleration (HorvathAA), intrinsic epigenetic age acceleration (IEAA), Hannum's DNAm age acceleration (HannumAA), extrinsic epigenetic age acceleration (EEAA), GrimAge acceleration (GrimAA), and PhenoAge acceleration (PhenoAA). Mixed-effects modeling was used to assess the within-pair association between depression and DNAm age acceleration.
Results: At baseline, a 10-unit higher BDI-II total score was associated with HannumAA (0.73 years, 95% confidence interval [CI] 0.13-1.33, p = .019) and EEAA (0.94 years, 95% CI 0.22-1.66, p = .012). At follow-up, 10-unit higher BDI-II score was associated with PhenoAA (1.32 years, 95% CI 0.18-2.47, p = .027).
Conclusion: We identified that depression is associated with higher levels of DNAm age acceleration. Further investigation is warranted to better understand the underlying mechanisms for the potential causal relationship between depression and accelerated aging.

CAUSAL EFFECT OF AGE AT MENARCHE ON THE RISK FOR DEPRESSION: RESULTS FROM A TWO-SAMPLE MULTIVARIABLE MENDELIAN RANDOMIZATION STUDY

Hirtz R, Hars C, Naaresh R, Laabs BH, Antel J, Grasemann C, Hinney A, Hebebrand J, Peters T. Causal Effect of Age at Menarche on the Risk for Depression: Results From a Two-Sample Multivariable Mendelian Randomization Study. Front Genet. 2022 Jul 12;13:918584. doi: 10.3389/fgene.2022.918584. PMID: 35903354; PMCID: PMC9315288.

A fair number of epidemiological studies suggest that age at menarche (AAM) is associated with depression, but the reported effect sizes are small, and there is evidence of residual confounding. Moreover, previous Mendelian randomization (MR) studies to avoid inferential problems inherent to epidemiological studies have provided mixed findings. To clarify the causal relationship between age at menarche and broadly defined depression risk, we used 360 genome-wide significantly AAM-related single-nucleotide polymorphisms (SNPs) as instrumental variable and data from the latest GWAS for the broadly defined depression risk on 807,553 individuals (246,363 cases and 561,190 controls). Multiple methods to account for

heterogeneity of the instrumental variable (penalized weighted median, MR Lasso, and contamination mixture method), systematic and idiosyncratic pleiotropy (MR RAPS), and horizontal pleiotropy (MR PRESSO and multivariable MR using three methods) were used. Body mass index, education attainment, and total white blood count were considered pleiotropic phenotypes in the multivariable MR analysis. In the univariable [inverse-variance weighted (IVW): OR = 0.96, 95% confidence interval = 0.94–0.98, p = 0.0003] and multivariable MR analysis (IVW: OR = 0.96, 95% confidence interval = 0.94–0.99, p = 0.007), there was a significant causal effect of AAM on depression risk. Thus, the present study supports conclusions from previous epidemiological studies implicating AAM in depression without the pitfalls of residual confounding and reverse causation. Considering the adverse consequences of an earlier AAM on mental health, this finding should foster efforts to address risk factors that promote an earlier AAM.

AT-HOME, SUBLINGUAL KETAMINE TELEHEALTH IS A SAFE AND EFFECTIVE TREATMENT FOR MODERATE TO SEVERE ANXIETY AND DEPRESSION: FINDINGS FROM A LARGE, PROSPECTIVE, OPEN-LABEL EFFECTIVENESS TRIAL

Hull TD, Malgaroli M, Gazzaley A, Akiki TJ, Madan A, Vando L, Arden K, Swain J, Klotz M, Paleos C. At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: Findings from a large, prospective, open-label effectiveness trial. J Affect Disord. 2022 Oct 1;314:59-67. doi: 10.1016/j.jad.2022.07.004. Epub 2022 Jul 6. PMID: 35809678.

Background: At-home Ketamine-assisted therapy (KAT) with psychosocial support and remote monitoring through telehealth platforms addresses access barriers, including the COVID-19 pandemic. Large-scale evaluation of this approach is needed for questions regarding safety and effectiveness for depression and anxiety.

Methods: In this prospective study, a large outpatient sample received KAT over four weeks through a telehealth provider. Symptoms were assessed using the Patient Health Questionnaire (PHQ-9) for depression, and the Generalized Anxiety Disorder scale (GAD-7) for anxiety. Demographics, adverse events, and patient-reported dissociation were also analyzed. Symptom trajectories were identified using Growth Mixture Modeling, along with outcome predictors.

Results: A sample of 1247 completed treatment with sufficient data, 62.8 % reported a 50 % or greater improvement on the PHQ-9, d = 1.61, and 62.9 % on the GAD-7, d = 1.56. Remission rates were 32.6 % for PHQ-9 and 31.3 % for GAD-7, with 0.9 % deteriorating on the PHQ-9, and 0.6 % on the GAD-7. Four patients left treatment early due to side effects or clinician disqualification, and two more due to adverse events. Three patient subpopulations emerged, characterized by Improvement (79.3 %), Chronic (11.4 %), and Delayed Improvement (9.3 %) for

PHQ-9 and GAD-7. Endorsing side effects at Session 2 was associated with delayed symptom improvement, and Chronic patients were more likely than the other two groups to report dissociation at Session 4.

Conclusion: At-home KAT response and remission rates indicated rapid and significant antidepressant and anxiolytic effects. Rates were consistent with laboratory- and clinic-administered ketamine treatment. Patient screening and remote monitoring maintained low levels of adverse events. Future research should assess durability of effects

CONTINUING, REDUCING, SWITCHING, OR STOPPING ANTIPSYCHOTICS IN INDIVIDUALS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS WHO ARE CLINICALLY STABLE: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS.

Ostuzzi G, Vita G, Bertolini F, Tedeschi F, De Luca B, Gastaldon C, Nosé M, Papola D, Purgato M, Del Giovane C, Correll CU, Barbui C. Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis. Lancet Psychiatry. 2022 Aug;9(8):614-624. doi: 10.1016/S2215-0366(22)00158-4. Epub 2022 Jun 23. PMID: 35753323.

Background: Although antipsychotic maintenance treatment is widely recommended to prevent relapse in chronic psychoses, evidence-based guidelines do not provide clear indications on different maintenance treatment strategies, including continuing the antipsychotic at standard doses, reducing the dose, switching to another antipsychotic, or even stopping the antipsychotic. We aimed to compare the effectiveness of these maintenance treatment strategies, hypothesising the superiority of all strategies over stopping, and of continuing at standard doses over both switching and reducing the dose.
Methods: We did a systematic review and network meta-analysis of randomized controlled trials (RCTs) that investigated antipsychotics for relapse prevention in adults with schizophrenia-spectrum disorders who were clinically stable, and which compared four treatment strategies: continuing the current antipsychotic at standard doses recommended for acute treatment; reducing the current antipsychotic dose; switching to a different antipsychotic; and stopping the antipsychotic and replacing it with placebo. We excluded RCTs with fewer than 25 individuals, a prerandomisation washout period greater than 4 weeks, a follow-up shorter than 6 weeks, and those recruiting treatment-resistant individuals. We searched MEDLINE, EMBASE, PsycINFO, CINAHL, CENTRAL, and online trial registers for published and unpublished RCTs from inception to Sept 1, 2021, combining terms describing all available antipsychotics, and terms describing continuation, maintenance, or long-term treatment for schizophrenia-spectrum disorders. Relative risks (RRs) and standardised mean differences were pooled using random-effects pairwise and network meta-analyses. We assessed risk of bias of each RCT with the Cochrane Risk-of-Bias 2 tool, and confidence of

pooled estimates with CINeMA. The primary outcome was relapse prevention. The study protocol was registered in advance in the Open Science Forum registry.
Findings: Of 3936 records identified, 119 records, reporting on 101 RCTs, were eligible, 98 of which (including 13 988 individuals) provided data that could be meta-analysed for at least one outcome. The mean proportion of female participants per study was 38% (range 0-100; median 39%, IQR 29-50), whereas for male participants it was 62% (range 0-100; median 61%, IQR 50-71), and the overall mean age was 38·8 years (range 23·2-63·9; median 39·3, IQR 35·0-43·9). Of the 98 RCTs meta-analysed, 89·8% were done in high-income and upper-middle-income countries. The ethnic group White or so-called Caucasian was the most represented (mean 56% participants per study), although this information was relatively scarce. All continuation strategies were significantly more effective in preventing relapse than stopping antipsychotic treatment, with a large risk reduction for continuing at standard doses (RR 0·37, 95% CI 0·32-0·43; number-needed-to-treat [NNT] 3·17, 95% CI 2·94-3·51) and antipsychotic switching (RR 0·44, 0·37-0·53; NNT 3·57, 3·17-4·25), and moderate risk reduction for dose reduction (RR 0·68, 0·51-0·90; NNT 6·25, 4·08-20·00). Continuing and switching antipsychotics did not differ significantly (RR 0·84, 0·69-1·02; with lower values favouring continuing), whereas reducing antipsychotic dose was outperformed by both continuing (RR 0·55, 0·42-0·71; NNT 4·44, 3·45-6·90) and switching (RR 0·65, 0·47-0·89; NNT 5·17, 3·77-18·18). Results were supported by moderate confidence of evidence and confirmed by secondary analyses and by several sensitivity and subgroup analyses, including removing studies with abrupt antipsychotic discontinuation or fast tapering (≤4 weeks). No tolerability differences emerged between treatment strategies. According to the Cochrane Risk-of-Bias tool, version 2, 16·8% of included RCTs had an overall high risk of bias for the primary outcome. We found moderate heterogeneity (τ^2=0·13; I^2=61%) and no overall incoherence for the primary analysis. Results were supported by moderate confidence of evidence and confirmed by secondary analyses.
Interpretation: Contrary to our original hypothesis, we found that continuing antipsychotic treatment at standard doses or switching to a different antipsychotic are similarly effective treatment strategies, whereas reducing antipsychotic doses below standard doses is associated with higher risk of relapse than the other two maintenance treatment strategies and should therefore be limited to selected cases. Despite limitations, including moderate heterogeneity and moderate certainty of evidence, these results are of pragmatic relevance for clinicians, and should support the update of evidence-based guidelines.

ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: DOSE-RESPONSE META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Wu H, Siafis S, Hamza T, Schneider-Thoma J, Davis JM, Salanti G, Leucht S. Antipsychotic-Induced Weight Gain: Dose-Response Meta-Analysis of Randomized Controlled Trials. Schizophr Bull. 2022 May 7;48(3):643-654. doi: 10.1093/schbul/sbac001. PMID: 35137229; PMCID: PMC9077426.

Background: Weight gain is among the most important side-effects of antipsychotics. It is, however, unclear whether it is associated with antipsychotic doses. We aimed to fill this gap with a dose-response meta-analysis.

Methods: We searched multiple electronic databases (last update search June 2021) for all fixed-dose studies that investigated 16 second-generation antipsychotics and haloperidol in adults with acute exacerbation of schizophrenia or with negative symptoms. We estimated the dose-response curves by conducting random-effects dose-response meta-analyses. We used the restricted cubic spline to model the dose-response relationship. The primary outcome was mean weight gain in kg from baseline to endpoint, the secondary outcome was the number of patients with clinically important weight gain.

Findings: Ninety-seven studies with 333 dose arms (36 326 participants) provided data for meta-analyses. Most studies were short-term with median duration of 6 weeks (range 4 to 26 weeks). In patients with acute exacerbation, amisulpride, aripiprazole, brexpiprazole, cariprazine, haloperidol, lumateperone, and lurasidone produced mild weight gain in comparison to placebo (mean difference at any dose≤1 kg), while more significant weight gain was observed by all other drugs. For most drugs, dose-response curves showed an initial dose-related increase in weight which plateaued at higher doses, while for others there was no plateau and some even had bell-shaped curves, meaning less weight gain to be associated with higher doses.

Interpretation: Second-generation antipsychotics do not only differ in their propensity to produce weight gain, but also in the shapes of their dose-response curves. This information is important for dosing decisions in clinical practice.

PERSISTENT CHILDHOOD AND ADOLESCENT ANXIETY AND RISK FOR PSYCHOSIS: A LONGITUDINAL BIRTH COHORT STUDY

Morales-Muñoz I, Palmer ER, Marwaha S, Mallikarjun PK, Upthegrove R. Persistent Childhood and Adolescent Anxiety and Risk for Psychosis: A Longitudinal Birth Cohort Study. Biol Psychiatry. 2022 Aug 15;92(4):275-282. doi: 10.1016/j.biopsych.2021.12.003. Epub 2021 Dec 13. PMID: 35151465; PMCID: PMC9302897

Background: Persistent anxiety in childhood and adolescence could represent a novel treatment target for psychosis, potentially targeting activation of stress pathways and secondary nonresolving inflammatory response. Here, we examined the association between persistent anxiety through childhood and adolescence with individuals with psychotic experiences (PEs) or who met criteria for psychotic disorder (PD) at age 24 years. We also investigated whether C-reactive protein mediated any association.

Methods: Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) were available in 8242 children at age 8 years, 7658 at age 10 years, 6906 at age 13 years, and 3889 at age 24 years. The Development and Well-Being Assessment was administered to capture child and adolescent anxiety. We created a composite score of generalized anxiety at ages 8, 10, and 13. PEs and PD were assessed at age 24, derived from the Psychosis-like Symptoms Interview. The mean of C-reactive protein at ages 9 and 15 years was used as a mediator.

Results: Individuals with persistent high levels of anxiety were more likely to develop PEs (odds ratio 2.02, 95% CI 1.26-3.23, p = .003) and PD at age 24 (odds ratio 4.23, 95% CI 2.27-7.88, p < .001). The mean of C-reactive protein at ages 9 and 15 mediated the associations of persistent anxiety with PEs (bias-corrected estimate -0.001, p = .013) and PD (bias-corrected estimate 0.001, p = .003).

Conclusions: Persistent high levels of anxiety through childhood and adolescence could be a risk factor for psychosis. Persistent anxiety is potentially related to subsequent psychosis via activation of stress hormones and nonresolving inflammation. These results contribute to the potential for preventive interventions in psychosis, with the novel target of early anxiety.

THE EMPOWER BLENDED DIGITAL INTERVENTION FOR RELAPSE PREVENTION IN SCHIZOPHRENIA: A FEASIBILITY CLUSTER RANDOMISED CONTROLLED TRIAL IN SCOTLAND AND AUSTRALIA

Gumley AI, Bradstreet S, Ainsworth J, Allan S, Alvarez-Jimenez M, Aucott L, Birchwood M, Briggs A, Bucci S, Cotton SM, Engel L, French P, Lederman R, Lewis S, Machin M, MacLennan G, McLeod H, McMeekin N, Mihalopoulos C, Morton E, Norrie J, Schwannauer M, Singh SP, Sundram S, Thompson A, Williams C, Yung AR, Farhall J, Gleeson J. The EMPOWER blended digital intervention for relapse prevention in schizophrenia: a feasibility cluster randomised controlled trial in Scotland and Australia. Lancet Psychiatry. 2022 Jun;9(6):477-486. doi: 10.1016/S2215-0366(22)00103-1. PMID: 35569503.

Background: Early warning signs monitoring by service users with schizophrenia has shown promise in preventing relapse but the quality of evidence is low. We aimed to establish the feasibility of undertaking a definitive randomised controlled trial to determine the effectiveness of a blended digital intervention for relapse prevention in schizophrenia.

Methods: This multicentre, feasibility, cluster randomised controlled trial aimed to compare Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery (EMPOWER) with treatment as usual in community mental health services (CMHS) in Glasgow and Melbourne. CMHS were the unit of randomisation, selected on the basis of those that probably had five or more care coordinators willing to participate. Participants were eligible if they were older than 16 years, had a schizophrenia or related diagnosis confirmed via case records, were able to provide informed consent, had contact with

CMHS, and had had a relapse within the previous 2 years. Participants were randomised within stratified clusters to EMPOWER or to continue their usual approach to care. EMPOWER blended a smartphone for active monitoring of early warning signs with peer support to promote self-management and clinical triage to promote access to relapse prevention. Main outcomes were feasibility, acceptability, usability, and safety, which was assessed through face-to-face interviews. App usage was assessed via the smartphone and self-report. Primary end point was 12 months. Participants, research assistants and other team members involved in delivering the intervention were not masked to treatment conditions. Assessment of relapse was done by an independent adjudication panel masked to randomisation group. The study is registered at ISRCTN (99559262).

Findings: We identified and randomised eight CMHS (six in Glasgow and two in Melbourne) comprising 47 care coordinators. We recruited 86 service users between Jan 19 and Aug 8, 2018; 73 were randomised (42 [58%] to EMPOWER and 31 [42%] to treatment as usual). There were 37 (51%) men and 36 (49%) women. At 12 months, main outcomes were collected for 32 (76%) of service users in the EMPOWER group and 30 (97%) of service users in the treatment as usual group. Of those randomised to EMPOWER, 30 (71%) met our a priori criterion of more than 33% adherence to daily monitoring that assumed feasibility. Median time to discontinuation of these participants was 31·5 weeks (SD 14·5). There were 29 adverse events in the EMPOWER group and 25 adverse events in the treatment as usual group. There were 13 app-related adverse events, affecting 11 people, one of which was serious. Fear of relapse was lower in the EMPOWER group than in the treatment as usual group at 12 months (mean difference -7·53 (95% CI -14·45 to 0·60; Cohen's d -0·53).

Interpretation: A trial of digital technology to monitor early warning signs blended with peer support and clinical triage to detect and prevent relapse appears to be feasible, safe, and acceptable. A further main trial is merited.

OUTCOMES DURING AND AFTER EARLY INTERVENTION SERVICES FOR FIRST-EPISODE PSYCHOSIS: RESULTS OVER 5 YEARS FROM THE RAISE-ETP SITE-RANDOMIZED TRIAL

Robinson DG, Schooler NR, Marcy P, Gibbons RD, Hendricks Brown C, John M, Mueser KT, Penn DL, Rosenheck RA, Addington J, Brunette MF, Correll CU, Estroff SE, Mayer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Gingerich S, Pipes R, Miller AL, Severe JB, Kane JM. Outcomes During and After Early Intervention Services for First-Episode Psychosis: Results Over 5 Years From the RAISE-ETP Site-Randomized Trial. Schizophr Bull. 2022 Jun 11:sbac053. doi: 10.1093/schbul/sbac053. Epub ahead of print. PMID: 35689478.

To examine long-term effects of early intervention services (EIS) for first-episode psychosis, we compared Heinrichs-Carpenter Quality of Life (QLS) and Positive and Negative Syndrome Scale

(PANSS) scores and inpatient hospitalization days over 5 years with data from the site-randomized RAISE-ETP trial that compared the EIS NAVIGATE (17 sites; 223 participants) and community care (CC) (17 sites; 181 participants). Inclusion criteria were: age 15-40 years; DSM-IV diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified; first psychotic episode; antipsychotic medication taken for ≤6 months. NAVIGATE-randomized participants could receive NAVIGATE from their study entry date until NAVIGATE ended when the last-enrolled NAVIGATE participant completed 2 years of treatment. Assessments occurred every 6 months. 61% of participants had assessments conducted ≥2 years; 31% at 5 years. Median follow-up length was CC 30 months and NAVIGATE 38 months. Primary analyses assumed data were not-missing-at-random (NMAR); sensitivity analyses assumed data were missing-at-random (MAR). MAR analyses found no significant treatment-by-time interactions for QLS or PANSS. NMAR analyses revealed that NAVIGATE was associated with a 13.14 (95%CI:6.92,19.37) unit QLS and 7.73 (95%CI:2.98,12.47) unit PANSS better improvement and 2.53 (95%CI:0.59,4.47) fewer inpatient days than CC (all comparisons significant). QLS and PANSS effect sizes were 0.856 and 0.70. NAVIGATE opportunity length (mean 33.8 (SD = 5.1) months) was not associated (P = .72) with QLS outcome; duration of untreated psychosis did not moderate (P = .32) differential QLS outcome. While conclusions are limited by the low rate of five-year follow-up, the data support long-term benefit of NAVIGATE compared to community care.

THE EFFECTIVENESS OF INTENSIVE HOME TREATMENT AS A SUBSTITUTE FOR HOSPITAL ADMISSION IN ACUTE PSYCHIATRIC CRISIS RESOLUTION IN THE NETHERLANDS: A TWO-CENTRE ZELEN DOUBLE-CONSENT RANDOMISED CONTROLLED TRIAL

Cornelis J, Barakat A, Blankers M, Peen J, Lommerse N, Eikelenboom M, Zoeteman J, Van H, Beekman ATF, Dekker J. The effectiveness of intensive home treatment as a substitute for hospital admission in acute psychiatric crisis resolution in the Netherlands: a two-centre Zelen double-consent randomised controlled trial. Lancet Psychiatry. 2022 Aug;9(8):625-635. doi: 10.1016/S2215-0366(22)00187-0. Epub 2022 Jun 30. PMID: 35779532.

Background: Although de-institutionalisation has been underway for decades, admission to hospital followed by low-intensity outpatient care remains the usual treatment for patients with an acute psychiatric crisis. Intensive home treatment has been developed for patients in a severe psychiatric crisis as an alternative to inpatient care. This study aimed to evaluate the potential of intensive home treatment to reduce bed-days and its clinical effectiveness compared with treatment as usual.

Methods: We did a two-armed, two-centre, open-label, Zelen, double-consent, pragmatic randomised controlled trial. Patients aged 18-65 years were recruited at the psychiatric emergency service and psychiatric emergency wards of the two major mental health institutions (Arkin and GGZ inGeest) in Amsterdam, the Netherlands. Patients diagnosed with at least one DSM-IV-TR or DSM-5 disorder and in a psychiatric crisis and for whom psychiatrists had indicated or completed a clinical admission could be included. Trained psychiatric emergency service and hospital professionals did the automated web-based pre-randomisation procedure upon first contact with the patient. A seeded pseudo-random number generator allocated patients (2:1) to intensive home treatment or treatment as usual. Informed consent was obtained after randomisation as soon as the patient was mentally capable within 14 days. Due to the nature of this study, patients and professionals were not masked to treatment. Intensive home treatment was tailored to the nature of the crisis and goals of patients and relatives, and developed in collaboration with them and a multidisciplinary professional team. All main analyses were intention-to-treat, and the primary outcome was the total number of admission days 12 months after randomisation. To investigate the effect of treatment conditions on the outcome measures, linear mixed modelling analyses using restricted maximum likelihood estimation were done. This trial was prospectively registered with Trialregister.nl, NL-6020 (NTR-6151).

Findings: Between Nov 15, 2016, and Oct 15, 2018, 246 patients were included in the study (183 patients with intensive home treatment vs 63 patients with treatment as usual). 135 women (55%) and 111 men (45%) were included, with a mean age of 41·01 years (range 18-65; SD 12·68). 114 participants (46%) were born in the Netherlands and 85 (35%) elsewhere (missing data on 47 [19%] participants). Ethnicity data were not available. After 12 months, the mean number of admission days in the intensive home treatment condition was 42·47 (SD 53·92) versus 67·02 (SD 79·03) for treatment as usual, a reduction of 24·55 days (SD 10·73) or 36·6% (p=0·033). 26 adverse events were registered, 23 (89%) of which were suicide attempts. The number of patients with a reported adverse event did not differ significantly between the groups (15 [8%] in the intensive home treatment group vs five [8%] in the treatment as usual group; p=0·950). Five patients died by suicide (three [2%] in the intensive home treatment group vs two [3%] in the treatment as usual group; p=0·610). No treatment-related deaths occurred.

Interpretation: Intensive home treatment is a safe and effective partial substitute for conventional psychiatric crisis care that led to a reduction in admission days, causing patients to stay longer in their social environment, with similar clinical effects, patient satisfaction and adverse events.

A SYSTEMATIC REVIEW OF RELATIONAL-BASED THERAPIES FOR THE TREATMENT OF AUDITORY HALLUCINATIONS IN PATIENTS WITH PSYCHOTIC DISORDERS

Dellazizzo L, Giguère S, Léveillé N, Potvin S, Dumais A. A systematic review of relational-based therapies for the treatment of auditory hallucinations in patients with psychotic disorders. Psychol Med. 2022 Jul 20;52(11):1-8. doi: 10.1017/S003329172200143X. Epub ahead of print. PMID: 35855651; PMCID: PMC9386435.

Background: Auditory hallucinations in patients with psychotic disorders may be very distressing. Unfortunately, a large proportion of individuals are resistant to pharmacological interventions and the gold-standard cognitive-behavioral therapy for psychosis offers at best modest effects. To improve therapeutic outcomes, several therapies have been created to establish a relationship between voice-hearers and their voices. With increasing literature, we conducted a systematic review of dialogical therapies and examined the evidence behind their efficacy.

Methods: A systematic search was performed in PubMed, PsycINFO, Web of Science, and Google Scholar. Articles were included if they discussed the effects of dialogical interventions for patients with psychotic disorders.

Results: A total of 17 studies were included within this systematic review. Cumulative evidence from various therapies has shown that entering in a dialog with voices is beneficial to patients, even those who are resistant to current pharmacological treatments. Heightened benefits have been mainly observed with Relating Therapy and Avatar Therapy/Virtual Reality assisted Therapy, with evidence generally of moderate quality. Both these interventions have shown large to very large effects on voices and voice-related distress as well as moderate to large magnitude improvements on affective symptoms. Though, cognitive-behavioral therapy for command hallucinations and making sense of voices noted no improvements on voices.

Conclusions: Literature on relational-based interventions with a strong emphasis on the relational aspects of voice hearing has shown positive effects. Results suggest that these dialogical therapies might surpass the efficacy of current gold-standard approaches.

DOPAMINERGIC DYSFUNCTION AND EXCITATORY/INHIBITORY IMBALANCE IN TREATMENT-RESISTANT SCHIZOPHRENIA AND NOVEL NEUROMODULATORY TREATMENT

Wada M, Noda Y, Iwata Y, Tsugawa S, Yoshida K, Tani H, Hirano Y, Koike S, Sasabayashi D, Katayama H, Plitman E, Ohi K, Ueno F, Caravaggio F, Koizumi T, Gerretsen P, Suzuki T, Uchida H, Müller DJ, Mimura M, Remington G, Grace AA, Graff-Guerrero A, Nakajima S. Dopaminergic dysfunction and excitatory/inhibitory imbalance in treatment-resistant schizophrenia and novel neuromodulatory treatment. Mol Psychiatry. 2022 Jul;27(7):2950-2967. doi: 10.1038/s41380-022-01572-0. Epub 2022 Apr 20. PMID: 35444257.

Antipsychotic drugs are the mainstay in the treatment of schizophrenia. However, one-third of patients do not show adequate improvement in positive symptoms with non-clozapine antipsychotics. Additionally, approximately half of them show poor response to clozapine, electroconvulsive therapy, or other augmentation strategies. However, the development of novel treatment for these conditions is difficult due to the complex and heterogenous pathophysiology of treatment-resistant schizophrenia (TRS). Therefore, this review provides key findings, potential treatments, and a roadmap for future research in this area. First, we review the neurobiological pathophysiology of TRS, particularly the dopaminergic, glutamatergic, and GABAergic pathways. Next, the limitations of existing and promising treatments are presented. Specifically, this article focuses on the therapeutic potential of neuromodulation, including electroconvulsive therapy, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation. Finally, we propose multivariate analyses that integrate various perspectives of the pathogenesis, such as dopaminergic dysfunction and excitatory/inhibitory imbalance, thereby elucidating the heterogeneity of TRS that could not be obtained by conventional statistics. These analyses can in turn lead to a precision medicine approach with closed-loop neuromodulation targeting the detected pathophysiology of TRS

BRIDGING KNOWLEDGE GAPS IN THE DIAGNOSIS AND MANAGEMENT OF NEUROPSYCHIATRIC SEQUELAE OF COVID-19

Frontera JA, Simon NM. Bridging Knowledge Gaps in the Diagnosis and Management of Neuropsychiatric Sequelae of COVID-19. JAMA Psychiatry. 2022 Jun 29. doi: 10.1001/jamapsychiatry.2022.1616. Epub ahead of print. PMID: 35767287.

Importance: Neuropsychiatric symptoms have been reported as a prominent feature of postacute sequelae of COVID-19 (PASC), with common symptoms that include cognitive impairment, sleep difficulties, depression, posttraumatic stress, and substance use disorders. A primary challenge of parsing PASC epidemiology and pathophysiology is the lack of a standard definition of the syndrome, and little is known regarding mechanisms of neuropsychiatric PASC.

Observations: Rates of symptom prevalence vary, but at least 1 PASC neuropsychiatric symptom has been reported in as many as 90% of patients 6 months after COVID-19 hospitalization and in approximately 25% of nonhospitalized adults with COVID-19. Mechanisms of neuropsychiatric sequelae of COVID-19 are still being elucidated. They may include static brain injury accrued during acute COVID-19, neurodegeneration triggered by secondary effects of acute COVID-19, autoimmune mechanisms with chronic inflammation, viral persistence in tissue reservoirs, or reactivation of other latent viruses. Despite rapidly emerging data, many gaps in knowledge persist related to the variable definitions of PASC, lack of standardized phenotyping or biomarkers, variability in virus genotypes, ascertainment

biases, and limited accounting for social determinants of health and pandemic-related stressors.

Conclusions and relevance: Growing data support a high prevalence of PASC neuropsychiatric symptoms, but the current literature is heterogeneous with variable assessments of critical epidemiological factors. By enrolling large patient samples and conducting state-of-the-art assessments, the Researching COVID to Enhance Recovery (RECOVER), a multicenter research initiative funded by the National Institutes of Health, will help clarify PASC epidemiology, pathophysiology, and mechanisms of injury, as well as identify targets for therapeutic intervention

ASSOCIATION BETWEEN SERUM LITHIUM LEVEL AND INCIDENCE OF COVID-19 INFECTION

De Picker LJ, Leboyer M, Geddes JR, Morrens M, Harrison PJ, Taquet M. Association between serum lithium level and incidence of COVID-19 infection. Br J Psychiatry. 2022 Jul;221(1):425-427. doi: 10.1192/bjp.2022.42. PMID: 35318909; PMCID: PMC7612897

An antiviral effect of lithium has been proposed, but never investigated for coronavirus disease 2019 (COVID-19). Using electronic health records of 26 554 patients with documented serum lithium levels during the pandemic, we show that the 6-month COVID-19 infection incidence was lower among matched patients with 'therapeutic' (0.50-1.00) versus 'subtherapeutic' (0.05-0.50) lithium levels (hazard ratio (HR) = 0.82, 95% CI 0.69-0.97, *P* = 0.017) and among patients with 'therapeutic' lithium levels versus matched patients using valproate (HR = 0.79, 95% CI 0.67-0.92, *P* = 0.0023). Lower rates of infection were observed for both new COVID-19 diagnoses and positive polymerase chain reaction tests, regardless of underlying psychiatric diagnosis and vaccination status

THE MENTAL HEALTH BURDEN OF RACIAL AND ETHNIC MINORITIES DURING THE COVID-19 PANDEMIC

Nguyen LH, Anyane-Yeboa A, Klaser K, Merino J, Drew DA, Ma W, Mehta RS, Kim DY, Warner ET, Joshi AD, Graham MS, Sudre CH, Thompson EJ, May A, Hu C, Jørgensen S, Selvachandran S, Berry SE, David SP, Martinez ME, Figueiredo JC, Murray AM, Sanders AR, Koenen KC, Wolf J, Ourselin S, Spector TD, Steves CJ, Chan AT. The mental health burden of racial and ethnic minorities during the COVID-19 pandemic. PLoS One. 2022 Aug 10;17(8):e0271661. doi: 10.1371/journal.pone.0271661. PMID: 35947543; PMCID: PMC9365178.

Racial/ethnic minorities have been disproportionately impacted by COVID-19. The effects of COVID-19 on the long-term mental health of minorities remains unclear. To evaluate differences in odds of screening positive for depression and anxiety among various racial and ethnic groups during the latter phase of the COVID-19 pandemic, we performed a cross-sectional analysis of 691,473 participants nested within the prospective smartphone-based COVID Symptom Study in the United States (U.S.) and United Kingdom (U.K). from February 23, 2021 to June 9, 2021. In the U.S. (n=57,187), compared to White participants, the multivariable odds ratios (ORs) for screening positive for depression were 1·16 (95% CI: 1·02 to 1·31) for Black, 1·23 (1·11 to 1·36) for Hispanic, and 1·15 (1·02 to 1·30) for Asian participants, and 1·34 (1·13 to 1·59) for participants reporting more than one race/other even after accounting for personal factors such as prior history of a mental health disorder, COVID-19 infection status, and surrounding lockdown stringency. Rates of screening positive for anxiety were comparable. In the U.K. (n=643,286), racial/ethnic minorities had similarly elevated rates of positive screening for depression and anxiety. These disparities were not fully explained by changes in leisure time activities. Racial/ethnic minorities bore a disproportionate mental health burden during the COVID-19 pandemic. These differences will need to be considered as health care systems transition from prioritizing infection control to mitigating long-term consequences.

DURATION OF THE EFFECTIVENESS OF NICOTINE ELECTRONIC CIGARETTES ON SMOKING CESSATION AND REDUCTION: SYSTEMATIC REVIEW AND META-ANALYSIS

Vanderkam P, Bonneau A, Kinouani S, Dzeraviashka P, Castera P, Besnier M, Binder P, Doux N, Jaafari N, Lafay-Chebassier C. Duration of the effectiveness of nicotine electronic cigarettes on smoking cessation and reduction: Systematic review and meta-analysis. Front Psychiatry. 2022 Aug 4;13:915946. doi: 10.3389/fpsyt.2022.915946. PMID: 35990084; PMCID: PMC9386078.

Background: The success of pharmacotherapies for smoking cessation in real-life remains limited, with a significant number of long-term relapses. Despite first promising results, the duration of the effectiveness of electronic cigarettes is still unknown. Our objective was to assess the duration of the effectiveness of electronic cigarettes on smoking cessation and reduction in daily smokers.

Methods: The databases EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and PUBMED were consulted until March 23, 2022. We selected only randomized controlled trials with daily adult smokers. The intervention was the nicotinic electronic cigarette *vs*. non-nicotine electronic cigarette or other validated pharmacotherapies (varenicline, bupropion and nicotine replacement therapy). The minimum duration of the intervention was 3 months, with a follow-up of at least 6 months. Two independent reviewers used the PRISMA guidelines. The primary endpoint was smoking cessation at the end of the intervention and follow-up periods confirmed by a reduction in expired CO < 10 ppm. The

reduction was defined as at least 50% of the initial consumption or by a decrease of daily mean cigarette consumption at the end of the intervention and follow-up periods.

Results: Abstinence at the end of the intervention and follow-up periods was significantly higher in the nicotine electronic cigarette group, compared to nicotine replacement therapy (NRT) [respectively: RR: 1.37 (CI 95%: 1.32-2.93) and RR: 1.49 (CI 95%: 1.14-1.95)] and to the non-nicotine electronic cigarette condition [respectively: RR: 1.97 (CI 95%: 1.18-2.68) and RR: 1.66 (CI 95%: 1.01-2.73)]. With regard to smoking reduction, the electronic cigarette with nicotine is significantly more effective than NRT at the end of the intervention and follow-up periods [respectively RR: 1.48 (CI 95%: 1.04-2.10) and RR: 1.47 (CI 95%: 1.18-1.82)] and non-nicotine electronic cigarette in the long term [RR: 1.31 (CI 95%: 1.02-1.68)].

Conclusions: This meta-analysis shows the duration of the effectiveness of the nicotine electronic cigarette *vs*. non-nicotine electronic cigarette and NRT on smoking cessation and reduction. There are still uncertainties about the risks of its long-term use and its potential role as a gateway into smoking, particularly among young people.

EFFECTS OF RESTRICTING SOCIAL MEDIA USAGE ON WELLBEING AND PERFORMANCE: A RANDOMIZED CONTROL TRIAL AMONG STUDENTS

Collis A, Eggers F. Effects of restricting social media usage on wellbeing and performance: A randomized control trial among students. PLoS One. 2022 Aug 24;17(8):e0272416. doi: 10.1371/journal.pone.0272416. PMID: 36001541; PMCID: PMC9401146.

Recent research has shown that social media services create large consumer surplus. Despite their positive impact on economic welfare, concerns are raised about the negative association between social media usage and well-being or performance. However, causal empirical evidence is still scarce. To address this research gap, we conduct a randomized controlled trial among students in which we track participants' daily digital activities over the course of three quarters of an academic year. In the experiment, we randomly allocate half of the sample to a treatment condition in which social media usage (Facebook, Instagram, and Snapchat) is restricted to a maximum of 10 minutes per day. We find that participants in the treatment group substitute social media for instant messaging and do not decrease their total time spent on digital devices. Contrary to findings from previous correlational studies, we do not find any significant impact of social media usage as it was defined in our study on well-being and academic success. Our results also suggest that antitrust authorities should consider instant messaging and social media services as direct competitors before approving acquisitions.

PERCENTAGE OF HEAVY DRINKING DAYS FOLLOWING PSILOCYBIN-ASSISTED PSYCHOTHERAPY VS PLACEBO IN THE TREATMENT OF ADULT PATIENTS WITH ALCOHOL USE DISORDER: A RANDOMIZED CLINICAL TRIAL

Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, Mennenga SE, O'Donnell K, Owens LT, Podrebarac S, Rotrosen J, Tonigan JS, Worth L. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022 Aug 24. doi: 10.1001/jamapsychiatry.2022.2096. Epub ahead of print. PMID: 36001306.

Importance: Although classic psychedelic medications have shown promise in the treatment of alcohol use disorder (AUD), the efficacy of psilocybin remains unknown.

Objective: To evaluate whether 2 administrations of high-dose psilocybin improve the percentage of heavy drinking days in patients with AUD undergoing psychotherapy relative to outcomes observed with active placebo medication and psychotherapy.

Design, setting, and participants: In this double-blind randomized clinical trial, participants were offered 12 weeks of manualized psychotherapy and were randomly assigned to receive psilocybin vs diphenhydramine during 2 day-long medication sessions at weeks 4 and 8. Outcomes were assessed over the 32-week double-blind period following the first dose of study medication. The study was conducted at 2 academic centers in the US. Participants were recruited from the community between March 12, 2014, and March 19, 2020. Adults aged 25 to 65 years with a DSM-IV diagnosis of alcohol dependence and at least 4 heavy drinking days during the 30 days prior to screening were included. Exclusion criteria included major psychiatric and drug use disorders, hallucinogen use, medical conditions that contraindicated the study medications, use of exclusionary medications, and current treatment for AUD.

Interventions: Study medications were psilocybin, 25 mg/70 kg, vs diphenhydramine, 50 mg (first session), and psilocybin, 25-40 mg/70 kg, vs diphenhydramine, 50-100 mg (second session). Psychotherapy included motivational enhancement therapy and cognitive behavioral therapy.

Main outcomes and measures: The primary outcome was percentage of heavy drinking days, assessed using a timeline followback interview, contrasted between groups over the 32-week period following the first administration of study medication using multivariate repeated-measures analysis of variance.

Results: A total of 95 participants (mean [SD] age, 46 [12] years; 42 [44.2%] female) were randomized (49 to psilocybin and 46 to diphenhydramine). One participant (1.1%) was American Indian/Alaska Native, 5 (5.3%) were Black, 16 (16.8%) were Hispanic, and 75 (78.9%) were non-Hispanic White. Of the 95 randomized participants, 93 received at least 1 dose of

study medication and were included in the primary outcome analysis. Percentage of heavy drinking days during the 32-week double-blind period was 9.7% for the psilocybin group and 23.6% for the diphenhydramine group, a mean difference of 13.9%; (95% CI, 3.0-24.7; F1,86 = 6.43; P = .01). Mean daily alcohol consumption (number of standard drinks per day) was also lower in the psilocybin group. There were no serious adverse events among participants who received psilocybin.

Conclusions and relevance: Psilocybin administered in combination with psychotherapy produced robust decreases in percentage of heavy drinking days over and above those produced by active placebo and psychotherapy. These results provide support for further study of psilocybin-assisted treatment for AUD.

MICRODOSING WITH PSILOCYBIN MUSHROOMS: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

Cavanna F, Muller S, de la Fuente LA, Zamberlan F, Palmucci M, Janeckova L, Kuchar M, Pallavicini C, Tagliazucchi E. Microdosing with psilocybin mushrooms: a double-blind placebo-controlled study. Transl Psychiatry. 2022 Aug 2;12(1):307. doi: 10.1038/s41398-022-02039-0. PMID: 35918311; PMCID: PMC9346139.

The use of low sub-perceptual doses of psychedelics ("microdosing") has gained popularity in recent years. Although anecdotal reports claim multiple benefits associated with this practice, the lack of placebo-controlled studies severely limits our knowledge of microdosing and its effects. Moreover, research conducted in standard laboratory settings could fail to capture the motivation of individuals engaged or planning to engage in microdosing protocols, thus underestimating the likelihood of positive effects on creativity and cognitive function. We recruited 34 individuals starting to microdose with psilocybin mushrooms (Psilocybe cubensis), one of the materials most frequently used for this purpose. Following a double-blind placebo-controlled experimental design, we investigated the acute and short-term effects of 0.5 g of dried mushrooms on subjective experience, behavior, creativity (divergent and convergent thinking), perception, cognition, and brain activity. The reported acute effects were significantly more intense for the active dose compared to the placebo, but only for participants who correctly identified their experimental condition. These changes were accompanied by reduced EEG power in the theta band, together with preserved levels of Lempel-Ziv broadband signal complexity. For all other measurements there was no effect of microdosing except for few small changes towards cognitive impairment. According to our findings, low doses of psilocybin mushrooms can result in noticeable subjective effects and altered EEG rhythms, but without evidence to support enhanced well-being, creativity and cognitive function. We conclude that expectation underlies at least some of the anecdotal benefits attributed to microdosing with psilocybin mushrooms.

AGE-RELATED DIFFERENCES IN THE EFFECT OF CHRONIC ALCOHOL ON COGNITION AND THE BRAIN: A SYSTEMATIC REVIEW

Kuhns L, Kroon E, Lesscher H, Mies G, Cousijn J. Age-related differences in the effect of chronic alcohol on cognition and the brain: a systematic review. Transl Psychiatry. 2022 Aug 25;12(1):345. doi: 10.1038/s41398-022-02100-y. PMID: 36008381; PMCID: PMC9411553.

Adolescence is an important developmental period associated with increased risk for excessive alcohol use, but also high rates of recovery from alcohol use-related problems, suggesting potential resilience to long-term effects compared to adults. The aim of this systematic review is to evaluate the current evidence for a moderating role of age on the impact of chronic alcohol exposure on the brain and cognition. We searched Medline, PsycInfo, and Cochrane Library databases up to February 3, 2021. All human and animal studies that directly tested whether the relationship between chronic alcohol exposure and neurocognitive outcomes differs between adolescents and adults were included. Study characteristics and results of age-related analyses were extracted into reference tables and results were separately narratively synthesized for each cognitive and brain-related outcome. The evidence strength for age-related differences varies across outcomes. Human evidence is largely missing, but animal research provides limited but consistent evidence of heightened adolescent sensitivity to chronic alcohol's effects on several outcomes, including conditioned aversion, dopaminergic transmission in reward-related regions, neurodegeneration, and neurogenesis. At the same time, there is limited evidence for adolescent resilience to chronic alcohol-induced impairments in the domain of cognitive flexibility, warranting future studies investigating the potential mechanisms underlying adolescent risk and resilience to the effects of alcohol. The available evidence from mostly animal studies indicates adolescents are both more vulnerable and potentially more resilient to chronic alcohol effects on specific brain and cognitive outcomes. More human research directly comparing adolescents and adults is needed despite the methodological constraints. Parallel translational animal models can aid in the causal interpretation of observed effects. To improve their translational value, future animal studies should aim to use voluntary self-administration paradigms and incorporate individual differences and environmental context to better model human drinking behavior.

NITROUS OXIDE FOR THE TREATMENT OF PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW OF THE CLINICAL TRIAL LANDSCAPE

Liu H, Kerzner J, Demchenko I, Wijeysundera DN, Kennedy SH, Ladha KS, Bhat V. Nitrous oxide for the treatment of psychiatric disorders: A systematic review of the clinical trial landscape. Acta Psychiatr Scand. 2022 Aug;146(2):126-138. doi: 10.1111/acps.13432. Epub 2022 Apr 11. PMID: 35353901.

Objective: To systematically review published research studies and ongoing clinical trials investigating nitrous oxide (N_2 O) in psychiatric disorders, providing an up-to-date snapshot of the clinical research landscape.

Methods: A comprehensive literature search was conducted for studies published until June 2021 using the OVID databases (MEDLINE, Embase, APA PsycInfo) and the clinical trial registries (ClinicalTrials.gov, ICTRP).

Results: In total, five relevant published articles were identified, among which four investigated N_2 O for depression. One single-dose randomized controlled trial (RCT) for treatment-resistant depression (TRD), one triple crossover RCT comparing 50% vs. 25% N_2 O for TRD, and one repeated-dose RCT for major depressive disorder (MDD) suggest that N_2 O has preliminary feasibility with rapid-acting effects on symptoms of depression. From the public registries, 10 relevant ongoing clinical trials were identified. They aim to explore the use of N_2 O for MDD, post-traumatic stress disorder, bipolar disorder, obsessive-compulsive disorder, and suicidal ideation. To date, the typical treatment protocol parameters were a single session of 50% N_2 O delivered for 60 min, although the concentration of 25% is also being explored. Projected enrolment numbers for ongoing trials (M = 55.0) were much higher than sample sizes for published studies (M = 13.0), suggesting that there potentially will be more large-scale RCTs published in the next few years.

Conclusion: Preliminary studies support the feasibility of administering N_2 O for depression; however, appropriate blinding is a critical challenge. Larger-scale RCTs with repeated doses of N_2 O and follow-up times beyond 1 month are needed to confirm the feasibility, therapeutic efficacy, and sustainability of response.

INVOLVEMENT OF THE BRAIN-HEART AXIS IN THE LINK BETWEEN PTSD AND CARDIOVASCULAR DISEASE

Seligowski AV, Webber TK, Marvar PJ, Ressler KJ, Philip NS. Involvement of the brain-heart axis in the link between PTSD and cardiovascular disease. Depress Anxiety. 2022 Jun 16. doi: 10.1002/da.23271. Epub ahead of print. PMID: 35708302.

Posttraumatic stress disorder (PTSD) has long been associated with a heightened risk of cardiovascular disease (CVD). A number of mechanisms have been implicated to underlie this brain-heart axis relationship, such as altered functioning of the autonomic nervous system and increased systemic inflammation. While neural alterations have repeatedly been observed in PTSD, they are rarely considered in the PTSD-CVD link. The brain-heart axis is a pathway connecting frontal and limbic brain regions to the brainstem and periphery via the autonomic nervous system and it may be a promising model for understanding CVD risk in PTSD given its overlap with PTSD neural deficits. We first provide a summary of the primary mechanisms implicated in the association between PTSD and CVD. We then review the brain-heart axis and its relevance to PTSD, as well as findings from PTSD trials demonstrating that a number of PTSD treatments have effects on areas of the brain-heart axis. Finally, we discuss sex considerations in the PTSD-CVD link. A critical next step in this study is to determine if PTSD treatments that affect the brain-heart axis (e.g., brain stimulation that improves autonomic function) also reduce the risk of CVD.

EVALUATION OF INFERENCE-BASED COGNITIVE-BEHAVIORAL THERAPY FOR OBSESSIVE-COMPULSIVE DISORDER: A MULTICENTER RANDOMIZED CONTROLLED TRIAL WITH THREE TREATMENT MODALITIES

Aardema F, Bouchard S, Koszycki D, Lavoie ME, Audet JS, O'Connor K. Evaluation of Inference-Based Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder: A Multicenter Randomized Controlled Trial with Three Treatment Modalities. Psychother Psychosom. 2022;91(5):348-359. doi: 10.1159/000524425. Epub 2022 May 18. PMID: 35584639.

Introduction: Inference-based cognitive-behavioral therapy (I-CBT) is a specialized psychological treatment for obsessive-compulsive disorder (OCD) without deliberate and prolonged exposure and response prevention (ERP) that focuses on strengthening reality-based reasoning and correcting the dysfunctional reasoning giving rise to erroneous obsessional doubts and ideas.

Objective: The present study aimed to evaluate the effectiveness of I-CBT through a comparison with appraisal-based cognitive behavioral therapy (A-CBT) and an adapted mindfulness-based stress reduction (MBSR) intervention.

Methods: This was a two-site, parallel-arm randomized controlled trial (RCT) comparing I-CBT with A-CBT. The MBSR intervention acted as a non-specific active control condition. Following formal evaluation, 111 participants diagnosed with OCD were randomly assigned. The principal outcome measure was the Yale-Brown Obsessive-Compulsive Scale.

Results: All treatments significantly reduced general OCD severity and specific symptom dimensions without a significant difference between treatments. I-CBT was associated with significant reductions in all symptom dimensions at post-test. Also, I-CBT led to significantly greater improvement in overvalued ideation, as well as significantly higher rates of remission as compared to MBSR at mid-test.

Conclusions: I-CBT and MBSR appear to be effective, alternative treatment options for those with OCD that yield similar outcomes as A-CBT. I-CBT may have an edge in terms of the rapidity by which patients reach remission, its generalizability across symptom dimension, its potentially higher level of acceptability, and effectiveness for overvalued ideation. Future research is needed to assess whether additional alternative treatments options can help to increase the number of people successfully treated.

COGNITIVE AND NEUROPSYCHIATRIC EFFECTS OF NORADRENERGIC TREATMENT IN ALZHEIMER'S DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS.

David MCB, Del Giovane M, Liu KY, Gostick B, Rowe JB, Oboh I, Howard R, Malhotra PA. Cognitive and neuropsychiatric effects of noradrenergic treatment in Alzheimer's disease: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2022 Jul 5:jnnp-2022-329136. doi: 10.1136/jnnp-2022-329136. Epub ahead of print. PMID: 35790417.

Background: Dysfunction of the locus coeruleus-noradrenergic system occurs early in Alzheimer's disease, contributing to cognitive and neuropsychiatric symptoms in some patients. This system offers a potential therapeutic target, although noradrenergic treatments are not currently used in clinical practice.
Objective: To assess the efficacy of drugs with principally noradrenergic action in improving cognitive and neuropsychiatric symptoms in Alzheimer's disease.
Methods: The MEDLINE, Embase and ClinicalTrials.gov databases were searched from 1980 to December 2021. We generated pooled estimates using random effects meta-analyses.
Results: We included 19 randomised controlled trials (1811 patients), of which six were judged as 'good' quality, seven as 'fair' and six 'poor'. Meta-analysis of 10 of these studies (1300 patients) showed a significant small positive effect of noradrenergic drugs on global cognition, measured using the Mini-Mental State Examination or Alzheimer's Disease Assessment Scale-Cognitive Subscale (standardised mean difference (SMD): 0.14, 95% CI: 0.03 to 0.25, p=0.01; I^2=0%). No significant effect was seen on measures of attention (SMD: 0.01, 95% CI: -0.17 to 0.19, p=0.91; I^2=0). The apathy meta-analysis included eight trials (425 patients) and detected a large positive effect of noradrenergic drugs (SMD: 0.45, 95% CI: 0.16 to 0.73, p=0.002; I^2=58%). This positive effect was still present following removal of outliers to account for heterogeneity across studies.
Discussion: Repurposing of established noradrenergic drugs is most likely to offer effective treatment in Alzheimer's disease for general cognition and apathy. However, several factors

should be considered before designing future clinical trials. These include targeting of appropriate patient subgroups and understanding the dose effects of individual drugs and their interactions with other treatments to minimise risks and maximise therapeutic effects.

OXIDATIVE STRESS MEDIATES THE ASSOCIATION BETWEEN DIETARY FAT INTAKE AND COGNITION IN US OLDER ADULTS

Liu D, Zhou L, Yang M, McIntyre RS, Cao B. Oxidative Stress Mediates the Association Between Dietary Fat Intake and Cognition in US Older Adults. Am J Geriatr Psychiatry. 2022 Jul;30(7):761-773. doi: 10.1016/j.jagp.2022.01.001. Epub 2022 Jan 14. PMID: 35151552.

Objective: Dietary fat intake was considered as a modifiable factor influencing cognitive performance. The objective was to 1) examine the associations between different types of dietary fat intakes and cognitive outcomes among elder adults (≥60 years old); 2) assess whether peripheral oxidative stress and antioxidant biomarkers are potential mediators of dietary fat intake and cognitive impairment relationship.

Methods: Using data from National Health and Nutrition Examination Survey 2011-2014, total fat, saturated fatty acid (SFAT), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), cholesterol, ω-3 and ω-6 fatty acids were used to evaluate dietary fat intakes. Cognitive outcomes were assessed by word learning and recall modules from the consortium to establish a registry for Alzheimer's Disease (CERAD), animal fluency test, and digit symbol substitution test (DSST). Antioxidant biomarkers were assessed by gamma glutamyl transpeptidase (GGT), bilirubin, uric acid, and vitamin D levels. Linear regression models and causal mediation analysis were applied to quantify the associations.

Results: A total of 2,253 elder adults were included in the data analyses. Dietary intake of PUFA and ω-6 fatty acid were positively associated with DSST [β (95% CI): 0.06 (0.01,0.10), t statistic = 2.39, df= 2238, p = 0.02; β (95% CI): 0.06 (0.01,0.11), t statistic = 2.54, df= 2238, p = 0.01, respectively]. GGT was negatively associated with DSST [β (95% CI): -0.04 (-0.07, -0.01), t statistic = -2.73, df= 2239, p = 0.01], whereas uric acid was positively associated with CERAD total score [β (95% CI): 0.04 (0.00,0.08), t statistic = 2.03, df= 2233, p = 0.04]. The association between dietary intake of PUFA/ω -3/ω -6 and DSST performance was partially mediated by GGT level.

Conclusion: Our findings support that PUFAs in dietary sources were associated with lower risks for cognitive impairment partially via lowering oxidative stress. Dietary PUFA supplementation may potentially reduce risk of cognitive impairment via antioxidative mechanism

THE EFFECTS OF BASELINE IMPAIRED GLOBAL COGNITIVE FUNCTION ON THE EFFICACY AND COGNITIVE EFFECTS OF ELECTROCONVULSIVE THERAPY IN GERIATRIC PATIENTS: A RETROSPECTIVE COHORT STUDY

Luccarelli J, Forester BP, Dooley M, Patrick RE, Harper DG, Seiner SJ, Petrides G, Mueller M, Henry ME. The Effects of Baseline Impaired Global Cognitive Function on the Efficacy and Cognitive Effects of Electroconvulsive Therapy in Geriatric Patients: A Retrospective Cohort Study. Am J Geriatr Psychiatry. 2022 Jul;30(7):790-798. doi: 10.1016/j.jagp.2021.12.008. Epub 2021 Dec 17. PMID: 34996701; PMCID: PMC9177530.

Objectives: This study explores the association between baseline impaired global cognitive function and changes in global cognitive function and depression among geriatric patients undergoing acute course electroconvulsive therapy (ECT).

Design: Retrospective cohort study.

Setting: Single freestanding psychiatric hospital.

Participants: Patients aged 50 and older receiving ECT.

Interventions: 10 ECT treatments.

Measurements: Cognitive assessments with the Montreal Cognitive Assessment (MoCA). Depression assessment with the Quick Inventory of Depressive Symptomatology Self Report 16 item scale (QIDS).

Results: Baseline and follow-up data were available for 684 patients. On average, patients with baseline normal cognition (MoCA ≥26; N = 371) had a decrease in MoCA of -1.44±0.26 points over the course of treatment, while those with baseline impaired global cognitive function (MoCA <26; N = 313) had an increase in MoCA of 1.72±0.25 points. Baseline cognitive status was not associated with a differential response on the QIDS.

Conclusions: Patients with baseline impaired global cognitive function did not demonstrate a worsening in cognition following ECT, and baseline global cognitive function was not associated with a differential change in depression with ECT. These results suggest that impaired global cognitive function should not be viewed as a contraindication to ECT in geriatric patients.

COMPLEX PERSISTENT BENZODIAZEPINE DEPENDENCE—WHEN BENZODIAZEPINE DEPRESCRIBING GOES AWRY

Peng L, Meeks TW, Blazes CK. Complex Persistent Benzodiazepine Dependence-When Benzodiazepine Deprescribing Goes Awry. JAMA Psychiatry. 2022 Jul 1;79(7):639-640. doi: 10.1001/jamapsychiatry.2022.1150. PMID: 35583897.

BLACK INDIVIDUALS ARE HARDEST HIT BY DRUG OVERDOSE DEATH INCREASES

Kuehn BM. Black Individuals Are Hardest Hit by Drug Overdose Death Increases. JAMA. 2022 Aug 23;328(8):702-703. doi: 10.1001/jama.2022.13702. PMID: 35997722.

THE NEED FOR ELECTRONIC HEALTH RECORDS TO SUPPORT DELIVERY OF BEHAVIORAL HEALTH PREVENTIVE SERVICES

Huffstetler AN, Epling J, Krist AH. The Need for Electronic Health Records to Support Delivery of Behavioral Health Preventive Services. JAMA. 2022 Aug 23;328(8):707-708. doi: 10.1001/jama.2022.13391. PMID: 35925570; PMCID: PMC9423001.

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