35 depression-relevant abstracts april '19 newsletter

(Caspi and Moffitt 2018; Dakwar, Nunes et al. 2018; Dudas, Malouf et al. 2018; Ford, Lacy et al. 2018; Frolkis, Vallerand et al. 2018; George 2018; Guglielmo, Hootman et al. 2018; Kessler, MacNeill et al. 2018; Lee, Chung et al. 2018; Mota Pereira and Fonte 2018; Parker 2018; Rottenberg, Devendorf et al. 2018; Rucker, Iliff et al. 2018; Steinberg, Laursen et al. 2018; Su, Tseng et al. 2018; Taggart, Eaton et al. 2018; Vera-Chang, St-Jacques et al. 2018; Vollbehr, Bartels-Velthuis et al. 2018; Wellman, Wilson et al. 2018; Williams, Heifets et al. 2018; Ashdown-Franks, Stubbs et al. 2019; Baziar, Aqamolaei et al. 2019; Chamberlain, Cavanagh et al. 2019; Chiu, Yu et al. 2019; Conde-Sala, Garre-Olmo et al. 2019; de Vries, Roest et al. 2019; Domany, Bleich-Cohen et al. 2019; Fowler, Madan et al. 2019; Johnston, Powell et al. 2019; Lee, Stockings et al. 2019; Løge-Hagen, Sæle et al. 2019; Maund, Stuart et al. 2019; Sarris, Byrne et al. 2019; Strawbridge, Carter et al. 2019; Undurraga, Sim et al. 2019; Valles-Colomer, Falony et al. 2019)

Ashdown-Franks, G., B. Stubbs, et al. (2019). ***"Handgrip strength and depression among 34,129 adults aged 50 years and older in six low- and middle-income countries."*** Journal of Affective Disorders 243: 448-454. http://www.sciencedirect.com/science/article/pii/S0165032718312801

Introduction Handgrip strength is a simple and inexpensive marker of health and mortality risk. It presents an ideal risk-stratifying method for use in low and middle-income countries (LMICs). There are, however, no population-based studies investigating the associations between handgrip strength and depression in LMICs. We aimed to assess these associations among community-dwelling middle-aged and older adults using nationally representative data from six LMICs. Method Cross-sectional data on individuals aged ≥ 50 years from the World Health Organization's Study on Global Ageing and Adult Health were analyzed. Depression was based on the Composite International Diagnostic Interview. Weak handgrip strength was defined as < 30 kg for men and < 20 kg for women using the average value of two handgrip measurements of the dominant hand. Multivariable logistic regression analysis was conducted. Results The sample included 34,129 individuals (62.4 ± 16.0 years; 52.1% female). The prevalence of weak handgrip strength and depression were 47.4% and 6.2%, respectively. Individuals with weak handgrip strength had a higher prevalence of depression than those without this condition (8.8% vs. 3.8%; p < 0.001). Across all countries, after adjustment for potential confounders, weak handgrip strength was associated with a 1.45 (95%CI = 1.12–1.88) times higher odds for depression, although some between-country differences were noted. Discussion Weaker handgrip strength is associated with higher odds for depression in LMICs. Future research should seek to establish the predictive value of this inexpensive measure for clinical use. Furthermore, interventional studies should examine if muscular strength can be a target of resistance-training interventions to address depressive symptoms in low-resourced settings.

Baziar, S., A. Aqamolaei, et al. (2019). ***"Crocus sativus l. Versus methylphenidate in treatment of children with attention-deficit/hyperactivity disorder: A randomized, double-blind pilot study."*** Journal of Child and Adolescent Psychopharmacology 0(0): null. https://www.liebertpub.com/doi/abs/10.1089/cap.2018.0146

(Available in free full text) Abstract Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood and adolescence. About 30% of patients do not respond to stimulants or cannot tolerate their side effects. Thus, alternative medication, like herbal medicine, should be considered. The aim of this trial is to compare the safety and efficacy of Crocus sativus (saffron) versus methylphenidate in improving symptoms of children with ADHD. Methods: In a 6-week randomized double-blind study, 54 patients (children 6–17 years old) with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of ADHD were randomly assigned to receive either 20–30 mg/d (20 mg/d for <30 kg and 30 mg/d for >30 kg) methylphenidate (MPH) or 20–30 mg/d saffron capsules depending on weight (20 mg/d for <30 kg and 30 mg/d for >30 kg). Symptoms were assessed using the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and weeks 3 and 6. Results: Fifty patients completed the trial. General linear model repeated measures showed no significant difference between the two groups on Parent and Teacher Rating Scale scores ($F = 0.749$, $df = 1.317$, $p = 0.425$, and $F = 0.249$, $df = 1.410$, $p = 0.701$, respectively). Changes in Teacher and Parent ADHD Rating Scale scores from baseline to the study end were not significantly different between the saffron group and the MPH group ($p = 0.731$ and $p = 0.883$, respectively). The frequency of adverse effects was similar between saffron and MPH groups. Conclusion: Short-term therapy with saffron capsule showed the same efficacy compared with methylphenidate. Nevertheless, larger controlled studies with longer treatment periods are necessary for future studies.

Caspi, A. and T. E. Moffitt (2018). ***"All for one and one for all: Mental disorders in one dimension."*** Am J Psychiatry 175(9): 831-844. https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2018.17121383

In both child and adult psychiatry, empirical evidence has now accrued to suggest that a single dimension is able to measure a person's liability to mental disorder, comorbidity among disorders, persistence of disorders over time, and severity of symptoms. This single dimension of general psychopathology has been termed "p," because it conceptually parallels a dimension already familiar to behavioral scientists and clinicians: the "g" factor of general intelligence. As the g dimension reflects low to high mental ability, the p dimension represents low to high psychopathology severity, with thought disorder at the extreme. The dimension of p unites all disorders. It influences present/absent status on hundreds of psychiatric symptoms, which modern nosological systems typically aggregate into dozens of distinct diagnoses, which in turn aggregate into three overarching domains, namely, the externalizing, internalizing, and psychotic experience domains, which finally aggregate into one dimension of psychopathology from low to high: p. Studies show that the higher a person scores on p, the worse that person fares on measures of family history of psychiatric illness, brain function, childhood developmental history, and adult life impairment. A dimension of p may help account for ubiquitous nonspecificity in psychiatry: multiple disorders share the same risk factors and biomarkers and often respond to the same therapies. Here, the authors summarize the history of the unidimensional idea, review modern research into p, demystify statistical models, articulate some implications of p for prevention and clinical practice, and outline a transdiagnostic research agenda. [AJP AT 175: Remembering Our Past As We Envision Our Future. October 1910: A Study of Association in InsanityGrace Helen Kent and A.J. Rosanoff: "No sharp distinction can be drawn between mental health and mental disease; a large collection of material shows a gradual and not an abrupt transition from the normal state to pathological states."(Am J Psychiatry 1910; 67(2):317–390)]

Chamberlain, S. R., J. Cavanagh, et al. (2019). ***"Treatment-resistant depression and peripheral c-reactive protein."*** The British Journal of Psychiatry 214(1): 11-19. https://www.cambridge.org/core/article/treatmentresistant-depression-and-peripheral-creactive-protein/D23E125023396A714C7AAB8372FA3155

(Available in free full text) Background C-reactive protein (CRP) is a candidate biomarker for major depressive disorder (MDD), but it is unclear how peripheral CRP levels relate to the heterogeneous clinical phenotypes of the disorder. AimTo explore CRP in MDD and its phenotypic associations. Method We recruited 102 treatment-resistant patients with MDD currently experiencing depression, 48 treatment-responsive patients with MDD not currently experiencing depression, 48 patients with depression who were not receiving medication and 54 healthy volunteers. High-sensitivity CRP in peripheral venous blood, body mass index (BMI) and questionnaire assessments of depression, anxiety and childhood trauma were measured. Group differences in CRP were estimated, and partial least squares (PLS) analysis explored the relationships between CRP and specific clinical phenotypes. Results Compared with healthy volunteers, BMI-corrected CRP was significantly elevated in the treatment-resistant group (P = 0.007; Cohen's d = 0.47); but not significantly so in the treatment-responsive (d = 0.29) and untreated (d = 0.18) groups. PLS yielded an optimal two-factor solution that accounted for 34.7% of variation in clinical measures and for 36.0% of variation in CRP. Clinical phenotypes most strongly associated with CRP and heavily weighted on the first PLS component were vegetative depressive symptoms, BMI, state anxiety and feeling unloved as a child or wishing for a different childhood. Conclusions CRP was elevated in patients with MDD, and more so in treatment-resistant patients. Other phenotypes associated with elevated CRP included childhood adversity and specific depressive and anxious symptoms. We suggest that patients with MDD stratified for proinflammatory biomarkers, like CRP, have a distinctive clinical profile that might be responsive to second-line treatment with anti-inflammatory drugs.

Chiu, T.-F., T.-M. Yu, et al. (2019). ***"Sequential risk of depression in children born prematurely: A nationwide population- based analysis."*** Journal of Affective Disorders 243: 42-47. http://www.sciencedirect.com/science/article/pii/S0165032718313351

Background Whether children born prematurely are at a high risk of depression is still unknown. The present study examined the risk of depression in children who were born prematurely, by analyzing a national cohort in Taiwan. Methods All premature births between January 1, 2000, and December 31, 2010, by using the Taiwan National Health Insurance Research Database. A total of 21,478 preterm children and 85,903 full-term children were enrolled in this study. Sex, level of urbanization of residential area, and parental occupation were considered. We included participants who received a diagnosis of depression in more than two clinical visits or were hospitalized due to depression. Results Preterm children had a 2.75-fold higher risk of depression than full-term children (95% confidence interval [CI] = 1.58–4.79, $p < 0.001$). Sex was not likely to be associated with depression in this study ($p = 0.95$). The lowest level of urbanization significantly contributed to the risk of depression in preterm children (adjusted hazard ratio = 6.8, 95% CI = 1.63–28.46, $p < 0.01$). Regarding parental occupation, preterm children whose parents had blue-collar and other occupations had a 3.4- and 6.06-fold higher risk of depression, respectively, compared with other children (blue-collar occupations: 95% CI = 1.04–11.15, $p < 0.05$; other occupations: 95% CI = 1.71–21.49, $p < 0.01$). Conclusions Preterm children had a 2.7-fold higher risk of depression than children born full-term. Early identification, timely psychiatric care, intervention strategies, and support for their families may reduce the complications of mental illness in preterm children.

Conde-Sala, J. L., J. Garre-Olmo, et al. (2019). ***"Course of depressive symptoms and associated factors in people aged 65+ in europe: A two-year follow-up."*** Journal of Affective Disorders 245: 440-450. http://www.sciencedirect.com/science/article/pii/S0165032718315015

Background The epidemiology of depressive disorders presents notable differences among European countries. The objectives of the study are to determine the prevalence, incidence, persistence and remission rates of depressive symptoms and to identify risk factors and differences between four European regions. Method Prospective cohort design using data from waves 5 and 6 (2013–15) of the Survey of Health, Ageing and Retirement in Europe. Sample size included 31,491 non-institutionalized adults aged 65+. Depressive symptoms were assessed using the EURO-D. Results The prevalence of depressive symptoms (EURO-D ≥4) was 29.8% and 31.5%in waves 5 and 6, respectively. The risk factors associated depressive symptoms were poorer self-rated health, loneliness, impairment in ADL, female gender and financial difficulties. Incidence was 6.62 (99.9% CI: 6.61–6.63)/100 person-years and the persistence and remission rates were 9.22 and 5.78, respectively. Regarding the differences between European regions, the incidence (4.93 to 7.43) and persistence (5.14 to 11.86) rates followed the same ascending order: Northern, Eastern, Continental and Southern. The remission presented higher rates in the Eastern and Southern (6.60–6.61) countries than in the Northern and Continental (4.45–5.31) ones. Limitations The EURO-D scale is unable to distinguish between clinically relevant depressive symptoms and major depression. Conclusion The risk factors related to the incidence of depressive symptoms differed across European regions. In countries of eastern and southern Europe the most important predictors were female gender and impairment in ADL. Poorer self-rated health and older age were more relevant in the Northern countries, and chronic diseases were a key factor in the Continental region.

Dakwar, E., E. V. Nunes, et al. (2018). ***"A sub-set of psychoactive effects may be critical to the behavioral impact of ketamine on cocaine use disorder: Results from a randomized, controlled laboratory study."*** Neuropharmacology 142: 270-276. http://www.sciencedirect.com/science/article/pii/S0028390818300054

Abstracts Efforts to translate sub-anesthetic ketamine infusions into widespread clinical use have centered around developing medications with comparable neurobiological activity, but with attenuated psychoactive effects so as to minimize the risk of behavioral toxicity and abuse liability. Converging lines of research, however, suggest that some of the psychoactive effects of sub-anesthetic ketamine may have therapeutic potential. Here, we assess whether a subset of these effects – the so-called mystical-type experience – mediates the effect of ketamine on craving and cocaine use in cocaine dependent research volunteers. We found that ketamine leads to significantly greater acute mystical-type effects (by Hood Mysticism Scale: HMS), dissociation (by Clinician Administered Dissociative States Scale: CADSS), and near-death experience phenomena (by the Near-Death Experience Scale: NDES), relative to the active control midazolam. HMS score, but not the CADSS or NDES score, was found to mediate the effect of ketamine on global improvement (decreased cocaine use and craving) over the post-infusion period. This is the first controlled study to show that mystical-type phenomena, long considered to have therapeutic potential, may work to impact decision-making and behavior in a sustained manner. These data suggest that an important direction for medication development is the identification of ketamine-like pharmacotherapy that is selectively psychoactive (as opposed to free of experiential effects entirely), so that mystical-type perspectival shifts are more reliably produced and factors lending to abuse or behavioral impairment are minimized. Future research can further clarify the relationship between medication-occasioned mystical-type effects and clinical benefit for different disorders. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

de Vries, Y. A., A. M. Roest, et al. (2019). ***"Predicting antidepressant response by monitoring early improvement of individual symptoms of depression: Individual patient data meta-analysis."*** The British Journal of Psychiatry 214(1): 4-10. https://www.cambridge.org/core/article/predicting-antidepressant-response-by-monitoring-early-improvement-of-individual-symptoms-of-depression-individual-patient-data-metaanalysis/C044107D0AB53B80490564E31132315C

Background Improvement in depression within the first 2 weeks of antidepressant treatment predicts good outcomes, but non-improvers can still respond or remit, whereas improvers often do not. Aims We aimed to investigate whether early improvement of individual depressive symptoms better predicts response or remission. Method We obtained individual patient data of 30 trials comprising 2184 placebo-treated and 6058 antidepressant-treated participants. Primary outcome was week 6 response; secondary outcomes were week 6 remission and week 12 response and remission. We compared models that only included improvement in total score by week 2 (total improvement model) with models that also included improvement in individual symptoms. Results For week 6 response, the area under the receiver operating characteristic curve and negative and positive predictive values of the total improvement model were 0.73, 0.67 and 0.74 compared with 0.77, 0.70 and 0.71 for the item improvement model. Model performance decreased for week 12 outcomes. Of predicted non-responders, 29% actually did respond by week 6 and 43% by week 12, which was decreased from the baseline (overall) probabilities of 51% by week 6 and 69% by week 12. In post hoc analyses with continuous rather than dichotomous early improvement, including individual items did not enhance model performance. Conclusions Examining individual symptoms adds little to the predictive ability of early improvement. Additionally, early non-improvement does not rule out response or remission, particularly after 12 rather than 6 weeks. Therefore, our findings suggest that routinely adapting pharmacological treatment because of limited early improvement would often be premature.

Domany, Y., M. Bleich-Cohen, et al. (2019). ***"Repeated oral ketamine for out-patient treatment of resistant depression: Randomised, double-blind, placebo-controlled, proof-of-concept study."*** The British Journal of Psychiatry 214(1): 20-26. https://www.cambridge.org/core/article/repeated-oral-ketamine-for-outpatient-treatment-of-resistant-depression-randomised-doubleblind-placebocontrolled-proofofconcept-study/76898B0B3980372F9EE79043F55A08FD

(Available in free full text) Background Ketamine has been demonstrated to improve depressive symptoms. Aims Evaluation of efficacy, safety and feasibility of repeated oral ketamine for out-patients with treatment-resistant depression (TRD). Method In a randomised, double-blind, placebo-controlled, proof-of-concept trial, 41 participants received either 1 mg/kg oral ketamine or placebo thrice weekly for 21 days (ClinicalTrials.gov Identifier: NCT02037503). Evaluation was performed at baseline, 40 and 240 min post administration and on days 3, 7, 14 and 21. The main outcome measure was change in Montgomery–Åsberg Depression Rating Scale (MADRS). Results Twenty-two participants were randomised to the ketamine group, and 19 to the control, with 82.5% (n = 33) completing the study. In the ketamine group, a decrease in depressive symptoms was evident at all time points, whereas in the control group a decrease was evident only 40 min post administration. The reduction in MADRS score on day 21 was 12.75 in the ketamine group versus 2.49 points with placebo ($P < 0.001$). Six participants in the ketamine group (27.3%) achieved remission compared with none of the controls ($P < 0.05$). The number needed to treat for remission was 3.7. Side-effects were mild and transient. Conclusions Repeated oral ketamine produced rapid and persistent amelioration of depressive symptoms in out-patients with TRD, and was well tolerated. These results suggest that add-on oral ketamine may hold significant promise in the care of patients suffering from TRD in the community.

Dudas, R., R. Malouf, et al. (2018). ***"Antidepressants for treating depression in dementia."*** Cochrane Database of Systematic Reviews(8). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003944.pub2/full

(Available in free full text(BACKGROUND: The use of antidepressants in dementia accompanied by depressive symptoms is widespread, but their clinical efficacy is uncertain. This review updates an earlier version, first published in 2002. OBJECTIVES: To determine the efficacy and safety of any type of antidepressant for patients who have been diagnosed as having dementia of any type and depression as defined by recognised criteria. SEARCH METHODS: We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's Specialised Register, on 16 August 2017. ALOIS contains information on trials retrieved from databases and from a number of trial registers and grey literature sources. SELECTION CRITERIA: We included all relevant double-blind, randomised trials comparing any antidepressant drug with placebo, for patients diagnosed as having dementia and depression. DATA COLLECTION AND ANALYSIS: Two review authors selected studies for inclusion and extracted data independently. We assessed risk of bias in the included studies using the Cochrane 'Risk of bias' tool. Where clinically appropriate, we pooled data for treatment periods up to three months and from three to nine months. We used GRADE methods to assess the overall quality of the evidence. MAIN RESULTS: We included ten studies with a total of 1592 patients. Eight included studies reported sufficiently detailed results to enter into analyses related to antidepressant efficacy. We split one study which included two different antidepressants and therefore had nine groups of patients treated with antidepressants compared with nine groups receiving placebo treatment. Information needed to make 'Risk of bias' judgements was often missing.We found high-quality evidence of little or no difference in scores on depression symptom rating scales between the antidepressant and placebo treated groups after 6 to 13 weeks (standardised mean difference (SMD) -0.10, 95% confidence interval (CI) -0.26 to 0.06; 614 participants; 8 studies). There was probably also little or no difference between groups after six to nine months (mean difference (MD) 0.59 point, 95% CI -1.12 to 2.3, 357 participants; 2 studies; moderate-quality evidence). The evidence on response rates at 12 weeks was of low quality, and imprecision in the result meant we were uncertain of any effect of antidepressants (antidepressant: 49.1%, placebo: 37.7%; odds ratio (OR) 1.71, 95% CI 0.80 to 3.67; 116 participants; 3 studies). However, the remission rate was probably higher in the antidepressant group than the placebo group (antidepressant: 40%, placebo: 21.7%; OR 2.57, 95% CI 1.44 to 4.59; 240 participants; 4 studies; moderate-quality evidence). The largest of these studies continued for another 12 weeks, but because of imprecision of the result we could not be sure of any effect of antidepressants on remission rates after 24 weeks. There was evidence of no effect of antidepressants on performance of activities of daily living at weeks 6 to 13 (SMD -0.05, 95% CI -0.36 to 0.25; 173 participants; 4 studies; high-quality evidence) and probably also little or no effect on cognition (MD 0.33 point on the Mini-Mental State Examination, 95% CI -1.31 to 1.96; 194 participants; 6 studies; moderate-quality evidence).Participants on antidepressants were probably more likely to drop out of treatment than those on placebo over 6 to 13 weeks (OR 1.51, 95% CI 1.07 to 2.14; 836 participants; 9 studies). The meta-analysis of the number of participants suffering at least one adverse event showed a significant difference in favour of placebo (antidepressant: 49.2%, placebo: 38.4%; OR 1.55, 95% CI 1.21 to 1.98, 1073 participants; 3 studies), as did the analyses for participants suffering one event of dry mouth (antidepressant: 19.6%, placebo: 13.3%; OR 1.80, 95% CI 1.23 to 2.63, 1044 participants; 5 studies), and one event of dizziness (antidepressant: 19.2%, placebo: 12.5%; OR 2.00, 95% CI 1.34 to 2.98, 1044 participants; 5 studies). Heterogeneity in the way adverse events were reported in studies presented a major difficulty for meta-analysis, but there was some evidence that antidepressant treatment causes more adverse effects than placebo treatment does. AUTHORS' CONCLUSIONS: The available evidence is of variable quality and does not provide strong support for the efficacy of antidepressants for treating depression in dementia, especially beyond 12 weeks. On the only measure of efficacy for which we had high-quality evidence (depression rating scale scores), antidepressants showed little or no effect. The evidence on remission rates favoured antidepressants but was of moderate quality, so future research may find a different result. There was insufficient evidence to draw conclusions about individual antidepressant drugs or about subtypes of dementia or depression. There is some evidence that antidepressant treatment may cause adverse events.

Ford, A. C., B. E. Lacy, et al. (2018). ***"Effect of antidepressants and psychological therapies in irritable bowel syndrome: An updated systematic review and meta-analysis."*** The American Journal of Gastroenterology. https://doi.org/10.1038/s41395-018-0222-5

Objectives Irritable bowel syndrome (IBS) is a chronic functional bowel disorder that is thought to be due to a disorder of brain–gut function. Drugs acting centrally, such as antidepressants, and psychological therapies may, therefore, be effective. Methods We updated a previous systematic review and meta-analysis of randomized controlled trials (RCTs). MEDLINE, EMBASE, PsychINFO, and the Cochrane Controlled Trials Register were searched (up to July 2017). Trials recruiting adults with IBS, which compared antidepressants versus placebo, or psychological therapies versus control therapy or "usual management" were eligible. Dichotomous symptom data were pooled to obtain a relative risk (RR) of remaining symptomatic after therapy, with a 95% confidence interval (CI). Results The search strategy identified 5316 citations. Fifty-three RCTs, reported in 51 separate articles, were eligible for inclusion: 17 compared antidepressants with placebo, 35 compared psychological therapies with control therapy or "usual management", and one compared both psychological therapy and antidepressants with placebo. Four of the trials of psychological therapies, and one of the RCTs of antidepressants, were identified since our previous meta-analysis. The RR of IBS symptoms not improving with antidepressants versus placebo was 0.66 (95% CI 0.57–0.76), with similar treatment effects for both tricyclic antidepressants and SSRIs, although with heterogeneity between RCTs of the latter ($I2 = 49\%$, $P = 0.07$). The RR of symptoms not improving with psychological therapies was 0.69 (95% CI 0.62–0.76). Cognitive behavioral therapy, relaxation therapy, multi-component psychological therapy, hypnotherapy, and dynamic psychotherapy were all beneficial when data from two or more RCTs were pooled. There was significant heterogeneity between studies ($I2 = 69\%$, $P < 0.001$) and significant funnel plot asymmetry. There were also issues regarding trial design, including lack of blinding. Conclusions Antidepressants are efficacious in reducing symptoms in IBS patients. Psychological therapies also appear to be effective treatments for IBS, although there are limitations in the quality of the evidence, and treatment effects may be overestimated as a result.

Fowler, J. C., A. Madan, et al. (2019). ***"Differentiating bipolar disorder from borderline personality disorder: Diagnostic accuracy of the difficulty in emotion regulation scale and personality inventory for dsm-5."*** Journal of Affective Disorders 245: 856-860. http://www.sciencedirect.com/science/article/pii/S0165032718316203

Background Confusion abounds when differentiating the diagnoses of bipolar disorder (BD) from borderline personality disorder (BPD). This study explored the relative clinical utility of affective instability and self-report personality trait measures for accurate identification of BD and BPD. Methods Receiver operator characteristics and diagnostic efficiency statistics were calculated to ascertain the relative diagnostic efficiency of self-report measures. Inpatients with research-confirmed diagnoses of BD ($n = 341$) or BPD ($n = 381$) completed the Difficulty in Emotion Regulation Scale (DERS) and Personality Inventory for DSM-5 (PID-5). Results The total score for DERS evidenced relatively poor accuracy for differentiating the disorders ($AUC = 0.72$, $SE = 0.02$, $p < .0001$), while subscales of affective instability measures yielded fair discrimination (AUC range = 0.70–0.59). The PID-5 BPD algorithm (consisting of emotional lability, anxiousness, separation insecurity, hostility, depressivity, impulsivity, and risk taking) evidenced moderate-to-excellent accuracy ($AUC = 0.83$, $SE = 0.04$, $p < .0001$) with a good balance of specificity ($SP = 0.79$) and sensitivity ($SN = 0.77$). Conclusion Findings support the use of the PID-5 algorithm for differentiating BD from BPD. Furthermore, findings support the accuracy of the DSM-5 alternative model Criteria B trait constellation for differentiating these two disorders with overlapping features.

Frolkis, A. D., I. A. Vallerand, et al. (2018). ***"Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression."*** Gut. https://gut.bmj.com/content/gutjnl/early/2018/10/18/gutjnl-2018-317182.full.pdf

Objective Depression is associated with IBD, but the effect of antidepressants on IBD has been sparsely studied. We assessed the impact of depression and antidepressant therapies on the development of IBD.Design The Health Improvement Network (THIN) was used to identify a cohort of patients with new-onset depression from 1986 to 2012. THIN patients who did not meet the defining criteria for depression were part of the referent group. The outcome was incident Crohn's disease (CD) or ulcerative colitis (UC). Cox proportional hazards modelling was performed to evaluate the rate of Crohn's disease or UC development among patients with an exposure of depression after controlling for age, sex, socioeconomic status, comorbid conditions, smoking, anxiety and antidepressant use including atypical antidepressants, mirtazapine, monoamine oxidase inhibitors (MAOI), serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), serotonin modulators; and tricyclic antidepressants (TCA).Results We identified 403 665 (7.05%) patients with incident depression. Individuals with depression had a significantly greater risk of developing CD (adjusted HR=2.11, 95% CI 1.65 to 2.70) and UC (adjusted HR=2.23, 95% CI 1.92 to 2.60) after controlling for demographic and clinical covariates. SSRI and TCA were protective against CD, whereas mirtazapine, SNRI, SSRI, serotonin modulators and TCA were protective for UC.Conclusion Patients with a history of depression were more likely to be diagnosed with IBD. In contrast, antidepressant treatments were selectively protective for Crohn's disease and UC. These results may impact counselling and management of depression and IBD.

George, M. S. (2018). ***"Is there really nothing new under the sun? Is low-dose ketamine a fast-acting antidepressant simply because it is an opioid?"*** Am J Psychiatry 175(12): 1157-1158. https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2018.18070800

(Available in free full text) Psychiatrists are now dealing with three "epidemics" that have a profound impact on society—opioid dependence, depression, and suicide. We desperately need new treatments for depression, and for suicidality, while also reducing opioid dependence and abuse. In the setting of this "triple crunch" and the frantic search for breakthrough treatments, low-dose intravenous ketamine has emerged as a potentially rapid-acting antidepressant that also quickly reduces suicidality. Could the universe be so cruel as to make it so that a treatment for one or two of the epidemics actually fuels the other? Thus, the article by Williams and colleagues (1) in this issue has potentially broad clinical and social implications, as it raises questions about all three. In this small-sample single-center crossover trial, these innovative Stanford researchers asked a simple but important question: Do the rapid antidepressant effects of ketamine depend on activation of opioid receptors? Specifically, can you block the antidepressant effect of ketamine by pretreatment with naltrexone, an opioid blocker? They asked this question in part because the other main pharmacological action of ketamine, N-methyl-D-aspartate (NMDA) receptor antagonism, has largely failed to emerge as the necessary mechanism of action for ketamine's antidepressant effects. The answer seems clear from this trial, which was stopped early because the distinct answer emerged with only half the projected sample. Pretreating with naltrexone dramatically blocked the antidepressant effect of ketamine, but it did not block the dissociation that many subjects experience. That is, ketamine's acute antidepressant effect appears to require opioid system activation. The succinct and logical conclusion from the research is that opioid receptors are necessary for ketamine's acute antidepressant effect.

Guglielmo, D., J. M. Hootman, et al. (2018). ***"Symptoms of anxiety and depression among adults with arthritis - united states, 2015-2017."*** MMWR. Morbidity and mortality weekly report 67(39): 1081-1087.
https://www.ncbi.nlm.nih.gov/pubmed/30286053
https://www.ncbi.nlm.nih.gov/pmc/PMC6171892/

(Available in free full text) An estimated 54.4 million (22.7%) U.S. adults have doctor-diagnosed arthritis (1). A report in 2012 found that, among adults aged ≥45 years with arthritis, approximately one third reported having anxiety or depression, with anxiety more common than depression (2). Studies examining mental health conditions in adults with arthritis have focused largely on depression, arthritis subtypes, and middle-aged and older adults, or have not been nationally representative (3). To address these knowledge gaps, CDC analyzed 2015-2017 National Health Interview Survey (NHIS) data* to estimate the national prevalence of clinically relevant symptoms of anxiety and depression among adults aged ≥18 years with arthritis. Among adults with arthritis, age-standardized prevalences of symptoms of anxiety and depression were 22.5% and 12.1%, respectively, compared with 10.7% and 4.7% among adults without arthritis. Successful treatment approaches to address anxiety and depression among adults with arthritis are multifaceted and include screenings, referrals to mental health professionals, and evidence-based strategies such as regular physical activity and participation in self-management education to improve mental health.

Johnston, K. M., L. C. Powell, et al. (2019). ***"The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature."*** Journal of Affective Disorders 242: 195-210.
http://www.sciencedirect.com/science/article/pii/S0165032718311200

(Available in free full text) Background Major depressive disorder (MDD) is a global public health concern. In particular, treatment-resistant depression (TRD) represents a key unmet need in the management of MDD. A systematic review of the epidemiological and economic literature on the burden associated with an increasing number of treatment steps due to TRD/non-response within an MDD episode was performed to quantify the burden of TRD. Methods Studies were identified in the PubMed/Medline databases through April 27th, 2017. Articles were limited to full-length peer-reviewed journal publications with no date restrictions. Economic and patient health-related quality of life (HRQoL) data on non-response by the number of treatment steps were quantified and, where appropriate, compared across studies; otherwise, comparative data within studies were reported. Results The 12 studies on economic burden found an association between increasing levels of TRD/non-response and elevations in direct and indirect costs. Likewise, the 19 studies studying HRQoL burden found that increasing levels of TRD/non-response correlated with reduced patient HRQoL and health status. Limitations TRD is defined inconsistently, which results in notable heterogeneity between published studies and poses methodological challenges for between-study comparisons. It is unknown if the increased economic and patient HRQoL burden are due to factors associated with TRD/non-response in addition to those due to depression persistence or severity. Conclusions A consistent trend was observed such that medical costs increased and patient HRQoL and health status decreased by increasing level of TRD/non-response within an MDD episode. These findings highlight the need for improved therapies for TRD to help reduce disease burden.

Kessler, D. S., S. J. MacNeill, et al. (2018). ***"Mirtazapine added to ssris or snris for treatment resistant depression in primary care: Phase iii randomised placebo controlled trial (mir)."*** British Medical Journal 363.
https://www.bmj.com/content/bmj/363/bmj.k4218.full.pdf

(Available in free full text) Objective To investigate the effectiveness of combining mirtazapine with serotonin-noradrenaline reuptake inhibitor (SNRI) or selective serotonin reuptake inhibitor (SSRI) antidepressants for treatment resistant depression in primary care. Design Two parallel group multicentre phase III randomised placebo controlled trial.Setting 106 general practices in four UK sites; Bristol, Exeter, Hull, and Keele/North Staffs, August 2013 to October 2015. Participants 480 adults aged 18 or more years who scored 14 or more on the Beck depression inventory, second revision, fulfilled ICD-10 (international classification of diseases, 10th revision) criteria for depression, and had used an SSRI or SNRI for at least six weeks but were still depressed. 241 were randomised to mirtazapine and 239 to placebo, both given in addition to usual SSRI or SNRI treatment. Participants were stratified by centre and minimised by baseline Beck depression inventory score, sex, and current psychological therapy. They were followed up at 12, 24, and 52 weeks. 431 (89.8%) were included in the (primary) 12 week follow-up. Main outcome measures Depressive symptoms at 12 weeks after randomisation, measured using the Beck depression inventory II score as a continuous variable. Secondary outcomes included measures of anxiety, quality of life, and adverse effects at 12, 24, and 52 weeks. Results Beck depression inventory II scores at 12 weeks were lower in the mirtazapine group after adjustment for baseline scores and minimisation or stratification variables, although the confidence interval included the null (mean (SD) scores at 12 weeks: 18.0 (12.3) in the mirtazapine group, 19.7 (12.4) in the placebo group; adjusted difference between means −1.83 (95% confidence interval −3.92 to 0.27); P=0.09). Adverse effects were more common in the mirtazapine group and were associated with the participants stopping the trial drug. Conclusion This study did not find evidence of a clinically important benefit for mirtazapine in addition to an SSRI or SNRI over placebo in a treatment resistant group of primary care patients with depression. This remains an area of important unmet need where evidence of effective treatment options is limited.Trial registration Current Controlled Trials ISRCTN06653773.

Lee, S. B., S. Chung, et al. (2018). ***"The mutual relationship between men's drinking and depression: A 4-year longitudinal analysis."*** Alcohol and Alcoholism 53(5): 597-602. http://dx.doi.org/10.1093/alcalc/agy003

Aims The purpose of the current study was to examine the longitudinal reciprocal relationship between depression and drinking among male adults from the general population. Methods This study used a panel dataset from the Korean Welfare Panel (from 2011 to 2014). The subjects were 2511 male adults aged between 20 and 65 years. Based on the Korean Version of the Alcohol Use Disorders Identification Test (AUDIT-K) scores, 2191 subjects were categorized as the control group (AUDIT-K < 12) and 320 subjects were categorized as the problem drinking group (AUDIT-K ≥ 12). An autoregressive cross-lagged modelling analysis was performed to investigate the mutual relationship between problem drinking and depression measured consecutively over time. Results The results indicated that alcohol drinking and depression were stable over time. In the control group, there was no significant causal relationship between problem drinking and depression while in the problem drinking group, drinking in the previous year significantly influenced depression in the following second, third and fourth years. Conclusion This study compared normal versus problem drinkers and showed a 4-year mutual causal relationship between depression and drinking. No longitudinal interaction between drinking and depression occurred in normal drinkers, while drinking intensified depression over time in problem drinkers. Short summary This study found that problem drinking was a risk factor for development of depression. Therefore, more attention should be given to problem alcohol use in the general population and evaluation of past alcohol use history in patients with depressive disorders.

Lee, Y. Y., E. A. Stockings, et al. (2019). ***"The risk of developing major depression among individuals with subthreshold depression: A systematic review and meta-analysis of longitudinal cohort studies."*** Psychological Medicine 49(1): 92-102. https://www.cambridge.org/core/article/risk-of-developing-major-depression-among-individuals-with-

subthreshold-depression-a-systematic-review-and-metaanalysis-of-longitudinal-cohort-studies/81883160AE1672276792AC54D7661990

Background Studies have consistently shown that subthreshold depression is associated with an increased risk of developing major depression. However, no study has yet calculated a pooled estimate that quantifies the magnitude of this risk across multiple studies. Methods We conducted a systematic review to identify longitudinal cohort studies containing data on the association between subthreshold depression and future major depression. A baseline meta-analysis was conducted using the inverse variance heterogeneity method to calculate the incidence rate ratio (IRR) of major depression among people with subthreshold depression relative to non-depressed controls. Subgroup analyses were conducted to investigate whether IRR estimates differed between studies categorised by age group or sample type. Sensitivity analyses were also conducted to test the robustness of baseline results to several sources of study heterogeneity, such as the case definition for subthreshold depression. Results Data from 16 studies (n = 67 318) revealed that people with subthreshold depression had an increased risk of developing major depression (IRR = 1.95, 95% confidence interval 1.28–2.97). Subgroup analyses estimated similar IRRs for different age groups (youth, adults and the elderly) and sample types (community-based and primary care). Sensitivity analyses demonstrated that baseline results were robust to different sources of study heterogeneity. Conclusion The results of this study support the scaling up of effective indicated prevention interventions for people with subthreshold depression, regardless of age group or setting.

Løge-Hagen, J. S., A. Sæle, et al. (2019). ***"Prevalence of depressive disorder among patients with fibromyalgia: Systematic review and meta-analysis."*** Journal of Affective Disorders 245: 1098-1105. http://www.sciencedirect.com/science/article/pii/S0165032718318433

Background It is acknowledged that fibromyalgia (FM) as a medical (rheumatological) disorder and major depressive disorder (MDD) as a mental disorder often co-occurs, but the inconsistency is prevailing at study-level and no overall estimate of the co-occurrence exist. Aims This systematic review and meta-analysis aimed to estimate the overall point- and life-time prevalence of MDD among FM patients based on structured clinical interviews (SCI); and to estimate the point-prevalence of MDD among FM patients based on screening symptom scales (SSS). Method The electronical databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO were searched for papers that reported on prevalence of MDD among FM patients. Eligible studies were included in a random effects meta-analysis pooling the prevalence of depression. Results The literature search identified 11 eligible studies for the meta-analysis. For SCI, the overall pooled point-prevalence (PP) was 25% (95% CI 19 to 31%), and life-time prevalence (LP) was 65% (95% CI 59 to 71%). When estimating the PP with self-administered SSS the overall pooled PP was 45% (95% CI 32 to 59%), and a single clinician–administered SSS yielded a PP of 23% (95% CI 10 to 41%). There was low inconsistency for the SCI and high inconsistency for the SSS. Conclusion One fourth of all FM patients had MDD, and more than half experienced MDD during their life-time according to clinician-administered instruments. Prevalence of MDD was almost twice as high when using self-administered symptom scales and may be likely to overestimate the co-occurrence.

Maund, E., B. Stuart, et al. (2019). ***"Managing antidepressant discontinuation: A systematic review."*** Annals of Family Medicine 17(1): 52-60. http://www.annfammed.org/content/17/1/52.abstract

(Available in free full text) PURPOSE We aimed to determine the effectiveness of interventions to manage antidepressant discontinuation, and the outcomes for patients. METHODS We conducted a systematic review with narrative synthesis and meta-analysis of studies published to March 2017. Studies were eligible for inclusion if they were randomized controlled trials, quasi-experimental studies, or observational studies assessing interventions to facilitate discontinuation of antidepressants for depression in adults. Our primary outcomes were antidepressant discontinuation and discontinuation symptoms. Secondary outcomes were relapse/recurrence; quality of life; antidepressant reduction; and sexual, social, and occupational function. RESULTS Of 15 included studies, 12 studies (8 randomized controlled trials, 2 single-arm trials, 2 retrospective cohort studies) were included in the synthesis. None were rated as having high risk for selection or detection bias. Two studies prompting primary care clinician discontinuation with antidepressant tapering guidance found 6% and 7% of patients discontinued, vs 8% for usual care. Six studies of psychological or psychiatric treatment plus tapering reported cessation rates of 40% to 95%. Two studies reported a higher risk of discontinuation symptoms with abrupt termination. At 2 years, risk of relapse/recurrence was lower with cognitive behavioral therapy plus taper vs clinical management plus taper (15% to 25% vs 35% to 80%: risk ratio = 0.34; 95% CI, 0.18–0.67; 2 studies). Relapse/recurrence rates were similar for mindfulness-based cognitive therapy with tapering and maintenance antidepressants (44% to 48% vs 47% to 60%; 2 studies). CONCLUSIONS Cognitive behavioral therapy or mindfulness-based cognitive therapy can help patients discontinue antidepressants without increasing the risk of relapse/recurrence, but are resource intensive. More scalable interventions incorporating psychological support are needed.

Mota Pereira, J. and D. Fonte (2018). ***"Pets enhance antidepressant pharmacotherapy effects in patients with treatment resistant major depressive disorder."*** Journal of Psychiatric Research 104: 108-113. http://www.sciencedirect.com/science/article/pii/S002239561830164X

Treatment resistant major depressive disorder (TR-MDD) is a severe disease, with very low remission rates. The resistance to pharmacotherapy leads to the search of non-pharmacological alternative approaches. Animal therapy has been used in patients with psychiatric conditions and the results have been promising. However, there have been no studies in TR-MDD patients with pet adoption. This study assessed the impact of TR-MDD patients adopting a pet. Eighty patients were suggested to adopt a pet, and 33 accepted the challenge. Other 33 patients constituted the control group (did not accept the suggestion of pet adoption and did not already have a pet). All patients maintained their usual pharmacotherapy. All participants were evaluated at baseline, 4, 8 and 12 weeks for depressive symptoms using HAMD17 and GAF. Results show that the pet group had an improvement in HAMD17 and GAF scores as well as higher response and remission rates compared to the control group, where no patient responded or remitted. Therefore, pets can be used as an effective adjuvant to pharmacotherapy with regular medical appointments. [See too BPS Digest comment at https://tinyurl.com/ycjowbm3].

Parker, G. (2018). ***"The benefits of antidepressants: News or fake news?"*** The British Journal of Psychiatry 213(2): 454-455. https://www.cambridge.org/core/article/benefits-of-antidepressants-news-or-fake-news/687A4E815C8AB2E1CEE1020BF6E8CEBC

(Available in free full text) Although antidepressant drugs are commonly effective, several meta-analyses of antidepressant drug trials undertaken decades after their introduction suggested that they were effectively acting as placebos. A recent meta-analysis concluded that they were effective. Both conclusions have been widely taken up by the media. This paper seeks to explain the disconnect.

Rottenberg, J., A. R. Devendorf, et al. (2018). ***"The curious neglect of high functioning after psychopathology: The case of depression."*** Perspectives on Psychological Science 13(5): 549-566. https://journals.sagepub.com/doi/abs/10.1177/1745691618769868

We address a key issue at the intersection of emotion, psychopathology, and public health—the startling lack of attention to people who experience benign outcomes, and even flourish, after recovering from depression. A rereading of the epidemiological literature suggests that the orthodox view of depression as chronic, recurrent, and lifelong is overstated. A significant subset of people recover and thrive after depression, yet research on such individuals has been rare. To facilitate work on this topic, we present a generative research framework. This framework includes (a) a proposed definition of healthy end-state functioning that goes beyond a reduction in clinical symptoms, (b) recommendations for specific measures to assess high functioning, and (c) a road map for a research agenda aimed at discovering how and why people flourish after emotional disturbance. Given that depression remains the most burdensome health condition worldwide, focus on what makes these excellent outcomes possible has enormous significance for the public health.

Rucker, J. J. H., J. Iliff, et al. (2018). ***"Psychiatry & the psychedelic drugs. Past, present & future."*** Neuropharmacology 142: 200-218. http://www.sciencedirect.com/science/article/pii/S002839081730638X

(Available in free full text) The classical psychedelic drugs, including psilocybin, lysergic acid diethylamide and mescaline, were used extensively in psychiatry before they were placed in Schedule I of the UN Convention on Drugs in 1967. Experimentation and clinical trials undertaken prior to legal sanction suggest that they are not helpful for those with established psychotic disorders and should be avoided in those liable to develop them. However, those with so-called 'psychoneurotic' disorders sometimes benefited considerably from their tendency to 'loosen' otherwise fixed, maladaptive patterns of cognition and behaviour, particularly when given in a supportive, therapeutic setting. Pre-prohibition studies in this area were sub-optimal, although a recent systematic review in unipolar mood disorder and a meta-analysis in alcoholism have both suggested efficacy. The incidence of serious adverse events appears to be low. Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics (mostly psilocybin) in various non-psychotic psychiatric disorders. These have provided encouraging results that provide initial evidence of safety and efficacy, however the regulatory and legal hurdles to licensing psychedelics as medicines are formidable. This paper summarises clinical trials using psychedelics pre and post prohibition, discusses the methodological challenges of performing good quality trials in this area and considers a strategic approach to the legal and regulatory barriers to licensing psychedelics as a treatment in mainstream psychiatry. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Sarris, J., G. J. Byrne, et al. (2019). ***"Nutraceuticals for major depressive disorder- more is not merrier: An 8-week double-blind, randomised, controlled trial."*** Journal of Affective Disorders 245: 1007-1015. http://www.sciencedirect.com/science/article/pii/S0165032718314113

Background One of the most pressing questions in "Nutritional Psychiatry" is whether using combinations of different nutraceuticals with putative antidepressant activity may provide an enhanced synergistic antidepressant effect. Methods A phase II/III, Australian multi-site, 8-week, double-blind, RCT involving 158 outpatients with a DSM-5 diagnosis of MDD. The intervention consisted of a nutraceutical combination: S-adenosyl methionine; Folinic acid; Omega-3 fatty acids; 5-HTP, Zinc picolinate, and relevant co-factors versus placebo. The primary outcome was change in MADRS score. Hypothesis-driven analyses of potential moderators of response involving key SNPs, and BDNF were also conducted. Results Placebo was superior to the nutraceutical combination in reducing MADRS score (differential reduction -1.75 points), however a mixed linear model revealed a non-significant Group X Time interaction ($p = 0.33$). Response rates were 40% for the active intervention and 51% for the placebo; remission rates were 34% and 43% for active and placebo groups, respectively. No significant differences were found between groups on any other secondary depression, anxiety, psychosocial, or sleep outcome measures. Key SNPs and BDNF did not significantly moderate response. No significant differences occurred between groups for total adverse effects, aside from more nausea in the active group. Limitations Very high placebo response rates suggest a placebo run-in design may have been valuable. Interpretation The adoption of a nutraceutical 'shotgun' approach to treating MDD was not supported, and appeared to be less effective than adding placebo to treatment as usual.

Steinberg, J. R., T. M. Laursen, et al. (2018). ***"Examining the association of antidepressant prescriptions with first abortion and first childbirth."*** JAMA Psychiatry 75(8): 828-834. http://dx.doi.org/10.1001/jamapsychiatry.2018.0849

Importance The repercussions of abortion for mental health have been used to justify state policies that limit access to abortion in the United States. Much earlier research has relied on self-report of abortion or mental health conditions or on convenience samples. This study uses data that rely on neither. Objective To examine whether first-trimester first abortion or first childbirth is associated with an increase in women's initiation of a first-time prescription for an antidepressant.Design, Setting, and Participants This study linked data and identified a cohort of women from Danish population registries who were born in Denmark between January 1, 1980, and December 30, 1994. Overall, 396 397 women were included in this study; of these women, 30 834 had a first-trimester first abortion and 85 592 had a first childbirth. Main Outcomes and Measure First-time antidepressant prescription redemptions were determined and used as indication of an episode of depression or anxiety, and incident rate ratios (IRRs) were calculated comparing women who had an abortion vs women who did not have an abortion and women who had a childbirth vs women who did not have a childbirth. Results Of 396 397 women whose data were analyzed, 17 294 (4.4%) had a record of at least 1 first-trimester abortion and no children, 72 052 (18.2%) had at least 1 childbirth and no abortions, 13 540 (3.4%) had at least 1 abortion and 1 childbirth, and 293 511 (74.1%) had neither an abortion nor a childbirth. A total of 59 465 (15.0%) had a record of first antidepressant use. In the basic and fully adjusted models, relative to women who had not had an abortion, women who had a first abortion had a higher risk of first-time antidepressant use. However, the fully adjusted IRRs that compared women who had an abortion with women who did not have an abortion were not statistically different in the year before the abortion (IRR, 1.46; 95% CI, 1.38-1.54) and the year after the abortion (IRR, 1.54; 95% CI, 1.45-1.62) ($P = .10$) and decreased as time from the abortion increased (1-5 years: IRR, 1.24; 95% CI, 1.19-1.29; >5 years: IRR, 1.12; 95% CI, 1.05-1.18). The fully adjusted IRRs that compared women who gave birth with women who did not give birth were lower in the year before childbirth (IRR, 0.47; 95% CI, 0.43-0.50) compared with the year after childbirth (IRR, 0.93; 95% CI, 0.88-0.98) ($P < .001$) and increased as time from the childbirth increased (1-5 years: IRR, 1.52; 95% CI, 1.47-1.56; >5 years: IRR, 1.99; 95% CI, 1.91-2.09). Across all women in the sample, the strongest risk factors associated with antidepressant use in the fully adjusted model were having a previous psychiatric contact (IRR, 3.70; 95% CI, 3.62-3.78), having previously obtained an antianxiety medication (IRR, 3.03; 95% CI, 2.99-3.10), and having previously obtained antipsychotic medication (IRR, 1.88; 95% CI, 1.81-1.96). Conclusions and Relevance Women who have abortions are more likely to use antidepressants compared with women who do not have abortions. However, additional aforementioned findings from this study support the conclusion that increased use of antidepressants is not attributable to having had an abortion but to differences in risk factors for depression. Thus, policies based on the notion that abortion harms women's mental health may be misinformed.

Strawbridge, R., B. Carter, et al. (2019). ***"Augmentation therapies for treatment-resistant depression: Systematic review and meta-analysis."*** The British Journal of Psychiatry 214(1): 42-51. https://www.cambridge.org/core/article/augmentation-therapies-for-treatmentresistant-depression-systematic-review-and-metaanalysis/0FEA123FDECE5FB2E838517DC22F8C57

(Available in free full text) Background Depression is considered to have the highest disability burden of all conditions. Although treatment-resistant depression (TRD) is a key contributor to that burden, there is little understanding of the best treatment approaches for it and specifically the effectiveness of available augmentation approaches. Aims We conducted a systematic review and meta-analysis to search and quantify the evidence of psychological and pharmacological augmentation interventions for TRD. Method Participants with TRD (defined as insufficient response to at least two antidepressants) were randomised to at least one augmentation treatment in the trial. Pre-post analysis assessed treatment effectiveness, providing an effect size (ES) independent of comparator interventions. Results Of 28 trials, 3 investigated psychological treatments and 25 examined pharmacological interventions. Pre-post analyses demonstrated N-methyl-d-aspartate-targeting drugs to have the highest ES (ES = 1.48, 95% CI 1.25–1.71). Other than aripiprazole (four studies, ES = 1.33, 95% CI 1.23–1.44) and lithium (three studies, ES = 1.00, 95% CI 0.81–1.20), treatments were each investigated in less than three studies. Overall, pharmacological (ES = 1.19, 95% CI 1.08–1.30) and psychological (ES = 1.43, 95% CI 0.50–2.36) therapies yielded higher ESs than pill placebo (ES = 0.78, 95% CI 0.66–0.91) and psychological control (ES = 0.94, 95% CI 0.36–1.52). Conclusions Despite being used widely in clinical practice, the evidence for augmentation treatments in TRD is sparse. Although pre-post meta-analyses are limited by the absence of direct comparison, this work finds promising evidence across treatment modalities.

Su, K., P. Tseng, et al. (2018). ***"Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms: A systematic review and meta-analysis."*** JAMA Network Open 1(5): e182327. http://dx.doi.org/10.1001/jamanetworkopen.2018.2327

(Available in free full text) Importance No systematic review or meta-analysis has assessed the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) for anxiety. Objective To evaluate the association of anxiety symptoms with omega-3 PUFA treatment compared with controls in varied populations.Data Sources PubMed, Embase, ProQuest, ScienceDirect, Cochrane Library, ClinicalKey, Web of Science, and ClinicalTrials.gov databases were searched up to March 4, 2018. Study Selection A search was performed of clinical trials assessing the anxiolytic effect of omega-3 PUFAs in humans, in either placebo-controlled or non–placebo-controlled designs. Of 104 selected articles, 19 entered the final data extraction stage.Data Extraction and Measures Two authors independently extracted the data according to a predetermined list of interests. A random-effects model meta-analysis was performed and this study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.Main Outcomes and Measures Changes in the severity of anxiety symptoms after omega-3 PUFA treatment. Results In total, 1203 participants with omega-3 PUFA treatment (mean age, 43.7 years; mean female proportion, 55.0%; mean omega-3 PUFA dosage, 1605.7 mg/d) and 1037 participants without omega-3 PUFA treatment (mean age, 40.6 years; mean female proportion, 55.0%) showed an association between clinical anxiety symptoms among participants with omega-3 PUFA treatment compared with control arms (Hedges g, 0.374; 95% CI, 0.081-0.666; P = .01). Subgroup analysis showed that the association of treatment with reduced anxiety symptoms was significantly greater in subgroups with specific clinical diagnoses than in subgroups without clinical conditions. The anxiolytic effect of omega-3 PUFAs was significantly better than that of controls only in subgroups with a higher dosage (at least 2000 mg/d) and not in subgroups with a lower dosage (<2000 mg/d). Conclusions and Relevance This review indicates that omega-3 PUFAs might help to reduce the symptoms of clinical anxiety. Further well-designed studies are needed in populations in whom anxiety is the main symptom.

Taggart, T. C., N. R. Eaton, et al. (2018). ***"Oral contraceptive use is associated with greater mood stability and higher relationship satisfaction."*** Neurology, Psychiatry and Brain Research 30: 154-162. http://www.sciencedirect.com/science/article/pii/S0941950018301763

Oral contraceptives (OCs) are one of the most commonly prescribed medications among women. OCs have been used to ameliorate hormone-related affective symptoms (e.g., mood lability). Previous data suggest that mood stability may have downstream effects for broader life outcomes, such as relationship satisfaction, which is also correlated with OC use. However, to date, no studies have examined the role of mood lability within the OC-relationship satisfaction association. Indirect effects structural equation modeling examined the extent to which OC use was associated with relationship satisfaction (direct effect), and the degree to which this association was mediated by mood lability (indirect effect) in women (N = 282) aged 18–32. OC users reported significantly higher relationship satisfaction (Cohen's d = .31) and less frequent occurrences of mood lability (d = .41) compared to non-users. Indirect effects suggested that mood lability accounted for nearly half of the variance in the OC-relationship satisfaction relationship. Findings support an emerging literature suggesting that, in addition to contraception, OC use may subsequently positively impact various domains of wellbeing for women and their families. Results support public policy efforts aimed at providing broad, affordable access to contraceptives, including for non-contraceptive benefits, and discussing OCs as a potential treatment with all women, including those not at imminent risk for pregnancy. Given their widespread use, availability, and low side effects profile, it is imperative that future research further elucidate non-contraceptive benefits associated with OC use. [See useful dicussion in BPS Digest - https://digest.bps.org.uk/2018/11/20/the-mood-stabilising-effect-of-taking-the-pill-has-downstream-benefits-for-womens-relationships-claims-new-study/]

Undurraga, J., K. Sim, et al. (2019). ***"Lithium treatment for unipolar major depressive disorder: Systematic review."*** Journal of Psychopharmacology 33(2): 167-176. https://journals.sagepub.com/doi/abs/10.1177/0269881118822161

Background:The potential value of lithium treatment in particular aspects of unipolar major depressive disorder remains uncertain.Methods:With reports of controlled trials identified by systematic searching of Medline, Cochrane Library, and PsycINFO literature databases, we summarized responses with lithium and controls followed by selective random-effects meta-analyses.Results:We identified 36 reports with 39 randomized controlled trials: six for monotherapy and 12 for adding lithium to antidepressants for acute major depression, and 21 for long-term treatment. Data for monotherapy of acute depression were few and inconclusive. As an adjunct to antidepressants, lithium was much more effective than placebo (p<0.0001). For long-term maintenance treatment, lithium was more effective than placebo in monotherapy (p=0.011) and to supplement antidepressants (p=0.038), and indistinguishable from antidepressant monotherapy.Conclusions:The findings indicate efficacy of lithium as a treatment for some aspects of major depressive disorder, especially as an add-on to antidepressants and for long-term prophylaxis. It remains uncertain whether some benefits of lithium treatment occur with many major depressive disorder patients, or if efficacy is particular to a subgroup with bipolar disorder-like characteristics or mixed-features.

Valles-Colomer, M., G. Falony, et al. (2019). ***"The neuroactive potential of the human gut microbiota in quality of life and depression."*** Nature Microbiology. https://doi.org/10.1038/s41564-018-0337-x

The relationship between gut microbial metabolism and mental health is one of the most intriguing and controversial topics in microbiome research. Bidirectional microbiota–gut–brain communication has mostly been explored in animal models,

with human research lagging behind. Large-scale metagenomics studies could facilitate the translational process, but their interpretation is hampered by a lack of dedicated reference databases and tools to study the microbial neuroactive potential. Surveying a large microbiome population cohort (Flemish Gut Flora Project, n = 1,054) with validation in independent data sets (ntotal = 1,070), we studied how microbiome features correlate with host quality of life and depression. Butyrate-producing Faecalibacterium and Coprococcus bacteria were consistently associated with higher quality of life indicators. Together with Dialister, Coprococcus spp. were also depleted in depression, even after correcting for the confounding effects of antidepressants. Using a module-based analytical framework, we assembled a catalogue of neuroactive potential of sequenced gut prokaryotes. Gut–brain module analysis of faecal metagenomes identified the microbial synthesis potential of the dopamine metabolite 3,4-dihydroxyphenylacetic acid as correlating positively with mental quality of life and indicated a potential role of microbial γ-aminobutyric acid production in depression. Our results provide population-scale evidence for microbiome links to mental health, while emphasizing confounder importance.

Vera-Chang, M. N., A. D. St-Jacques, et al. (2018). ***"Transgenerational hypocortisolism and behavioral disruption are induced by the antidepressant fluoxetine in male zebrafish danio rerio."*** PNAS: 201811695. https://www.pnas.org/content/pnas/early/2018/12/05/1811695115.full.pdf

Due to the high incidence of depression during childbearing, antidepressants such as fluoxetine (FLX) are highly prescribed during pregnancy, yet the risks to offspring are unknown. We report that a 6-day FLX exposure during early zebrafish development induces hypocortisolism for at least three generations. Gene expression analysis indicates that pathways controlling cortisol synthesis are altered in the descendants in the third generation. This FLX-induced low-cortisol phenotype is more prominent in males and is associated with significantly reduced exploratory behaviors for two generations. This is an important demonstration that, in an animal model, even a brief ancestral exposure to a common antidepressant modifies the stress response and critical coping behaviors for several generations.The global prevalence of depression is high during childbearing. Due to the associated risks to the mother and baby, the selective serotonin reuptake inhibitor fluoxetine (FLX) is often the first line of treatment. Given that FLX readily crosses the placenta, a fetus may be susceptible to the disruptive effects of FLX during this highly plastic stage of development. Here, we demonstrate that a 6-day FLX exposure to a fetus-relevant concentration at a critical developmental stage suppresses cortisol levels in the adult zebrafish (F0). This effect persists for three consecutive generations in the unexposed descendants (F1 to F3) without diminution and is more pronounced in males. We also show that the in vivo cortisol response of the interrenal (fish "adrenal") to an i.p. injection of adrenocorticotropic hormone was also reduced in the males from the F0 and F3 FLX lineages. Transcriptomic profiling of the whole kidney containing the interrenal cells revealed that early FLX exposure significantly modified numerous pathways closely associated with cortisol synthesis in the male adults from the F0 and F3 generations. We also show that the low cortisol levels are linked to significantly reduced exploratory behaviors in adult males from the F0 to F2 FLX lineages. This may be a cause for concern given the high prescription rates of FLX to pregnant women and the potential long-term negative impacts on humans exposed to these therapeutic drugs.

Vollbehr, N. K., A. A. Bartels-Velthuis, et al. (2018). ***"Hatha yoga for acute, chronic and/or treatment-resistant mood and anxiety disorders: A systematic review and meta-analysis."*** PLOS ONE 13(10): e0204925. https://doi.org/10.1371/journal.pone.0204925

(Available in free full text) Background The aim of this study was to systematically investigate the effectiveness of hatha yoga in treating acute, chronic and/or treatment-resistant mood and anxiety disorders. Methods Medline, Cochrane Library, Current Controlled Trials, Clinical Trials.gov, NHR Centre for Reviews and Dissemination, PsycINFO and CINAHL were searched through June 2018. Randomized controlled trials with patients with mood and anxiety disorders were included. Main outcomes were continuous measures of severity of mood and anxiety symptoms. Cohen's d was calculated as a measure of effect size. Meta-analyses using a random effects model was applied to estimate direct comparisons between yoga and control conditions for depression and anxiety outcomes. Publication bias was visually inspected using funnel plots. Results Eighteen studies were found, fourteen in acute patients and four in chronic patients. Most studies were of low quality. For depression outcomes, hatha yoga did not show a significant effect when compared to treatment as usual, an overall effect size of Cohen's d -0.64 (95% CI = -1.41, 0.13) or to all active control groups, Cohen's d -0.13 (95% CI = -0.49, 0.22). A sub-analysis showed that yoga had a significant effect on the reduction of depression compared to psychoeducation control groups, Cohen's d -0.52 (95% CI = -0.96, -0.08) but not to other active control groups, Cohen's d 0.28 (95% CI = -0.07, 0.63) For studies using a follow-up of six months or more, hatha yoga had no effect on the reduction of depression compared to active control groups, Cohen's d -0.14 (95% CI = -0.60, 0.33). Regarding anxiety, hatha yoga had no significant effect when compared to active control groups, Cohen's d -0.09 (95% CI = -0.47, 0.30). The I2 and Q-statistic revealed heterogeneity amongst comparisons. Qualitative analyses suggest some promise of hatha yoga for chronic populations. Conclusions The ability to draw firm conclusions is limited by the notable heterogeneity and low quality of most of the included studies. With this caveat in mind, the results of the current meta-analysis suggest that hatha yoga does not have effects on acute, chronic and/or treatment-resistant mood and anxiety disorders compared to treatment as usual or active control groups. However, when compared to psychoeducation, hatha yoga showed more reductions in depression. It is clear that more high-quality studies are needed to advance the field.

Wellman, R. J., K. M. Wilson, et al. (2018). ***"Secondhand smoke exposure and depressive symptoms in children: A longitudinal study."*** Nicotine & Tobacco Research: nty224-nty224. http://dx.doi.org/10.1093/ntr/nty224

Introduction We investigated whether secondhand smoke (SHS) exposure is associated with depressive symptoms in a population-based sample of children. Methods Never-smoking students from 29 French-language elementary schools in greater Montréal, Canada) were followed from 5th-11th grade (2005–11) in 5 waves: (1 (5th grade), 2 (spring 6th grade), 3 (7th grade), 4 (9th grade) and 5 (11th grade)). Associations between depressive symptoms and SHS exposure at home and in cars were examined in cross-sectional and longitudinal gamma generalized regression models adjusted for sex, maternal education and neighborhood socioeconomic status. Results The sample comprised 1553 baseline never smokers (Mean (SD) age = 10.7 (0.5) years; 44% male; 89% French-speaking). SHS exposure at home and in cars was associated with higher depressive symptom scores in cross-sectional analyses pooled across grades and adjusted for demographics (B (95% CI) = 0.041 (0.017, 0.068) for home exposure; 0.057 (0.030, 0.084) for car exposure). In longitudinal analyses from 5th to 6th grade, B (95% CI), adjusted for demographics and baseline depressive symptoms, was 0.042 (0.003, 0.080) for home exposure and 0.061 (0.019, 0.103) for car exposure. From 6th to 7th grade, B (95% CI) was 0.057 (0.003, 0.110) for home exposure and 0.074 (0.015, 0.133) for car exposure. SHS exposure at any age did not predict depressive symptoms two years later. Conclusions SHS exposure is associated with depressive symptoms in young persons, both concurrently and one year later. This finding adds to the evidence base supporting that children should be protected from SHS exposure.

Williams, N. R., B. D. Heifets, et al. (2018). ***"Attenuation of antidepressant effects of ketamine by opioid receptor antagonism."*** American Journal of Psychiatry 175(12): 1205-1215. https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2018.18020138

Objective: In addition to N-methyl-d-aspartate receptor antagonism, ketamine produces opioid system activation. The objective of this study was to determine whether opioid receptor antagonism prior to administration of intravenous ketamine attenuates its acute antidepressant or dissociative effects. Method:In a proposed double-blind crossover study of 30 adults with treatment-resistant depression, the authors performed a planned interim analysis after studying 14 participants, 12 of whom completed both conditions in randomized order: placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine. Response was defined as a reduction ≥50% in score on the 17-item Hamilton Depression Rating Scale (HAM-D) score on postinfusion day 1. Results:In the interim analysis, seven of 12 adults with treatment-resistant depression met the response criterion during the ketamine plus placebo condition. Reductions in 6-item and 17-item HAM-D scores among participants in the ketamine plus naltrexone condition were significantly lower than those of participants in the ketamine plus placebo condition on postinfusion days 1 and 3. Secondary analysis of all participants who completed the placebo and naltrexone conditions, regardless of the robustness of response to ketamine, showed similar results. There were no differences in ketamine-induced dissociation between conditions. Because naltrexone dramatically blocked the antidepressant but not the dissociative effects of ketamine, the trial was halted at the interim analysis. Conclusions:The findings suggest that ketamine's acute antidepressant effect requires opioid system activation. The dissociative effects of ketamine are not mediated by the opioid system, and they do not appear sufficient without the opioid effect to produce the acute antidepressant effects of ketamine in adults with treatment-resistant depression.