34 depression-relevant abstracts november '18 newsletter

(Bedi 2018; Bighelli, Castellazzi et al. 2018; Brookie, Best et al. 2018; Chiechio, Canonico et al. 2018; Dejonckheere, Mestdagh et al. 2018; Duan-Porter, Hatch et al. 2018; Furihata, Konno et al. 2018; Ghazizadeh-Hashemi, Ghajar et al. 2018; Goetter, Mauro et al. 2018; Grunebaum, Galfalvy et al. 2018; Hasin, Sarvet et al. 2018; Henssler, Kurschus et al. 2018; Henssler, Kurschus et al. 2018; Khambadkone, Cordner et al. 2018; Khandaker, Stochl et al. 2018; Lähteenvuo, Tanskanen et al. 2018; Lassale, Batty et al. 2018; Lopresti, Drummond et al. 2018; Lyall, Wyse et al. 2018; Meesters, Duijzer et al. 2018; Morrison, Law et al. 2018; Murrough, Huryk et al. 2018; Na, Yaramala et al. 2018; Nasca, Bigio et al. 2018; Pottie, Thompson et al. 2018; Rink, Braun et al. 2018; Schuch, Vancampfort et al. 2018; Swartz, Rucci et al. 2018; Veronese, Stubbs et al. 2018; Wang, Lin et al. 2018; Weinberger, Gbedemah et al. 2018; Willem van Dalen, van Wanrooij et al. 2018; Wilson, Cohen et al. 2018; Yu, Lim et al. 2018; Zhao, Ma et al. 2018)

Bedi, G. (2018). ***"3,4-methylenedioxymethamphetamine as a psychiatric treatment."*** JAMA Psychiatry 75(5): 419-420. http://dx.doi.org/10.1001/jamapsychiatry.2018.0063

Within 5 years, science will likely have answered a controversial question decades in the making: can the psychoactive drug commonly known as ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) be used to treat psychiatric disorders? After positive signals in 2 small trials of MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD)1,2 and unpublished phase 2 work, MDMA investigations are moving into phase 3. Moreover, MDMA-assisted psychotherapy has obtained the breakthrough therapy designation of the US Food and Drug Administration (FDA), which is intended to expedite development and review of novel, potentially effective treatments. The nonprofit organization coordinating this research, the Multidisciplinary Association for Psychedelic Studies (MAPS), estimates that phase 3 studies enrolling at least 200 participants will be completed by 2020, with a new drug application submitted to the FDA shortly thereafter. Of importance, the phase 3 protocols have undergone FDA special protocol assessment, increasing the chances of rapid approval in the event of positive results. Thus, MDMA may be approved for prescription by 2021, necessitating consideration of several important regulatory and clinical issues. Herein, I provide an overview of MDMA-assisted psychotherapy and key associated questions from the viewpoint that these issues need to be considered by psychiatry beyond the small community of MDMA therapy advocates.

Bighelli, I., M. Castellazzi, et al. (2018). ***"Antidepressants versus placebo for panic disorder in adults."*** Cochrane Database of Systematic Reviews(4). http://dx.doi.org/10.1002/14651858.CD010676.pub2

(Available in free full text) Background: Panic disorder is characterised by repeated, unexpected panic attacks, which represent a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes, and in which at least four of 13 characteristic symptoms are experienced, including racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness and breathlessness. It is common in the general population with a lifetime prevalence of 1% to 4%. The treatment of panic disorder includes psychological and pharmacological interventions. Amongst pharmacological agents, the National Institute for Health and Care Excellence (NICE) and the British Association for Psychopharmacology consider antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as the first-line treatment for panic disorder, due to their more favourable adverse effect profile over monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Several classes of antidepressants have been studied and compared, but it is still unclear which antidepressants have a more or less favourable profile in terms of effectiveness and acceptability in the treatment of this condition. Objectives: To assess the effects of antidepressants for panic disorder in adults, specifically: 1. to determine the efficacy of antidepressants in alleviating symptoms of panic disorder, with or without agoraphobia, in comparison to placebo; 2. to review the acceptability of antidepressants in panic disorder, with or without agoraphobia, in comparison with placebo; and 3. to investigate the adverse effects of antidepressants in panic disorder, with or without agoraphobia, including the general prevalence of adverse effects, compared to placebo. Search methods: We searched the Cochrane Common Mental Disorders' (CCMD) Specialised Register, and CENTRAL, MEDLINE, EMBASE and PsycINFO up to May 2017. We handsearched reference lists of relevant papers and previous systematic reviews. Selection criteria: All double-blind, randomised, controlled trials (RCTs) allocating adults with panic disorder to antidepressants or placebo. Data collection and analysis: Two review authors independently checked eligibility and extracted data using a standard form. We entered data into Review Manager 5 using a double-check procedure. Information extracted included study characteristics, participant characteristics, intervention details and settings. Primary outcomes included failure to respond, measured by a range of response scales, and treatment acceptability, measured by total number of dropouts for any reason. Secondary outcomes included failure to remit, panic symptom scales, frequency of panic attacks, agoraphobia, general anxiety, depression, social functioning, quality of life and patient satisfaction, measured by various scales as defined in individual studies. We used GRADE to assess the quality of the evidence for each outcome Main results: Forty-one unique RCTs including 9377 participants overall, of whom we included 8252 in the 49 placebo-controlled arms of interest (antidepressant as monotherapy and placebo alone) in this review. The majority of studies were of moderate to low quality due to inconsistency, imprecision and unclear risk of selection and performance bias. We found low-quality evidence that revealed a benefit for antidepressants as a group in comparison with placebo in terms of efficacy measured as failure to respond (risk ratio (RR) 0.72, 95% confidence interval (CI) 0.66 to 0.79; participants = 6500; studies = 30). The magnitude of effect corresponds to a number needed to treat for an additional beneficial outcome (NNTB) of 7 (95% CI 6 to 9): that means seven people would need to be treated with antidepressants in order for one to benefit. We observed the same finding when classes of antidepressants were compared with placebo. Moderate-quality evidence suggested a benefit for antidepressants compared to placebo when looking at number of dropouts due to any cause (RR 0.88, 95% CI 0.81 to 0.97; participants = 7850; studies = 30). The magnitude of effect corresponds to a NNTB of 27 (95% CI 17 to 105); treating 27 people will result in one person fewer dropping out. Considering antidepressant classes, TCAs showed a benefit over placebo, while for SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs) we observed no difference. When looking at dropouts due to adverse effects, which can be considered as a measure of tolerability, we found moderate-quality evidence showing that antidepressants as a whole are less well tolerated than placebo. In particular, TCAs and SSRIs produced more dropouts due to adverse effects in comparison with placebo, while the confidence interval for SNRI, noradrenergic reuptake inhibitors (NRI) and other antidepressants were wide and included the possibility of no difference. Authors' conclusions: The identified studies comprehensively address the objectives of the present review. Based on these results, antidepressants may be more effective than placebo in treating panic disorder. Efficacy can be quantified as a NNTB of 7, implying that seven people need to be treated with antidepressants in order for one to benefit. Antidepressants may also have benefit in comparison with placebo in terms of number of dropouts, but a less favourable profile in terms of dropout due to adverse effects. However, the tolerability profile varied between different classes of antidepressants. The choice of whether antidepressants should be prescribed in clinical practice cannot be made on the basis of this review. Limitations in results include funding of some studies by pharmaceutical companies, and only assessing short-term

outcomes. Data from the present review will be included in a network meta-analysis of psychopharmacological treatment in panic disorder, which will hopefully provide further useful information on this issue.

Brookie, K. L., G. I. Best, et al. (2018). ***"Intake of raw fruits and vegetables is associated with better mental health than intake of processed fruits and vegetables."*** Frontiers in Psychology 9(487). https://www.frontiersin.org/article/10.3389/fpsyg.2018.00487

(Available in free full text) Background: Higher intakes of fruits and vegetables, rich in micronutrients, have been associated with better mental health. However, cooking or processing may reduce the availability of these important micronutrients. This study investigated the differential associations between intake of raw fruits and vegetables, compared to processed (cooked or canned) fruits and vegetables, and mental health in young adults. Methods: In a cross-sectional survey design, 422 young adults ages 18 to 25 (66.1% female) living in New Zealand and the United States completed an online survey that assessed typical consumption of raw versus cooked/canned/processed fruits and vegetables, negative and positive mental health (depressive symptoms, anxiety, negative mood, positive mood, life satisfaction, and flourishing), and covariates (including socio-economic status, body mass index, sleep, physical activity, smoking, and alcohol use). Results: Controlling for covariates, raw fruit and vegetable intake predicted reduced depressive symptoms and higher positive mood, life satisfaction, and flourishing; processed fruit and vegetable intake only predicted higher positive mood. The top 10 raw foods related to better mental health were carrots, bananas, apples, dark leafy greens like spinach, grapefruit, lettuce, citrus fruits, fresh berries, cucumber, and kiwifruit. Conclusions: Raw FVI, but not processed FVI, significantly predicted higher mental health outcomes when controlling for the covariates. Applications include recommending the consumption of raw fruits and vegetables to maximise mental health benefits.

Chiechio, S., P. L. Canonico, et al. (2018). ***"L-acetylcarnitine: A mechanistically distinctive and potentially rapid-acting antidepressant drug."*** International journal of molecular sciences 19(1): 11. https://www.ncbi.nlm.nih.gov/pubmed/29267192 https://www.ncbi.nlm.nih.gov/pmc/PMC5795963/

Current therapy of mood disorders has several limitations. Although a high number of drugs are clinically available, as of today, nearly two-thirds of individuals do not achieve full symptomatic remission after treatment with conventional antidepressants. Moreover, several weeks of drug treatment are usually required to obtain clinical effects, a limitation that has considerable clinical implications, ranging from high suicide risk to reduced compliance. The characteristic lag time in classical antidepressant effectiveness has given great impulse to the search for novel therapeutics with more rapid effects. l-acetylcarnitine (LAC), a small molecule of growing interest for its pharmacological properties, is currently marketed for treatment of neuropathic pain. Recent preclinical and clinical data suggested that LAC may exert antidepressant effects with a more rapid onset than conventional drugs. Herein, we review data supporting LAC antidepressant activity and its distinctive mechanisms of action compared with monoaminergic antidepressants. Furthermore, we discuss the unique pharmacological properties of LAC that allow us to look at this molecule as representative of next generation antidepressants with a safe profile.

Dejonckheere, E., M. Mestdagh, et al. (2018). ***"The bipolarity of affect and depressive symptoms."*** J Pers Soc Psychol 114(2): 323-341. https://www.ncbi.nlm.nih.gov/pubmed/29389216

People differ in the extent to which they experience positive (PA) and negative affect (NA) rather independently or as bipolar opposites. Here, we examine the proposition that the nature of the relation between positive and negative affect in a person's emotional experience is indicative of psychological well-being, in particular the experience of depressive symptoms, typically characterized by diminished positive affect (anhedonia) and increased negative affect (depressed mood). In three experience sampling studies, we examine how positive and negative affective states are related within people's emotional experience in daily life and how the degree of bipolarity of this relation is associated with depressive symptom severity. In Study 1 and 2, we show both concurrently and longitudinally that a stronger bipolar PA-NA relationship is associated with, and in fact is predicted by, higher depressive symptom severity, even after controlling for mean levels of positive and negative affect. In Study 3, we replicate these findings in a daily diary design, with the two conceptually related main symptoms of depression, sadness, and anhedonia, as specific manifestations of high NA and low PA, respectively. Across studies, additional analyses indicate these results are robust across different time scales and various PA and NA operationalizations and that affective bipolarity shows particular specificity toward depressive symptomatology, in comparison with anxiety symptoms. Together, these findings demonstrate that depressive symptoms involve stronger bipolarity between positive and negative affect, reflecting reduced emotional complexity and flexibility.

Duan-Porter, W., D. Hatch, et al. (2018). ***"12-month trajectories of depressive symptoms among nurses—contribution of personality, job characteristics, coping, and burnout."*** Journal of Affective Disorders 234: 67-73. http://www.sciencedirect.com/science/article/pii/S016503271732253X

Background Job related factors have been associated with higher risk for developing depression, but past studies lacked full consideration of individual factors such as personality and coping. We sought to evaluate associations of personality, coping, job characteristics, and burnout with 12-month trajectories of depressive symptoms among nursing workers. Methods Cohort of nursing workers (N = 281) in a private hospital system, with baseline assessments of personality, job characteristics, and coping. Burnout and depression were measured at baseline and during monthly follow-ups. Linear mixed modeling was used to examine contributions to between- and within-individual variation in monthly depressive symptoms. Results Personality trait of negative affectivity accounted for 36% of between-individual variation in depressive symptoms over 12 months, while job characteristics and coping explained an additional 5% and 8% of this variation, respectively. Exhaustion dimension of burnout was associated with between-individual variation in depressive symptoms (fixed effect β coefficient 2.44, $p < 0.001$), but not with within-individual variation in symptoms. Disengagement dimension of burnout was not associated with between-individual variation in depressive symptoms, but contributed to within-individual variation in depressive symptoms over time (fixed effect β coefficient 0.52, $p = 0.01$). Limitations Participants were nursing workers within a single hospital system. Participants who were excluded due to missing baseline data were more likely of non-white race, which may also limit the generalizability of our results. We used latent variables to represent certain job and coping characteristics, which may make our results less comparable with other studies examining the role of these factors in work-associated depression. Conclusions Future interventions to prevent depression in healthcare workers should consider multiple job and individual factors. Potential components include strategies to manage negative affectivity and reduce avoidant coping, such as cognitive reframing and mindfulness-based techniques, and organizational approaches to address burnout through augmentation of job resources.

Furihata, R., C. Konno, et al. (2018). ***"Unhealthy lifestyle factors and depressive symptoms: A japanese general adult population survey."*** Journal of Affective Disorders 234: 156-161. http://www.sciencedirect.com/science/article/pii/S0165032717327155

Objective To investigate the relationship between unhealthy lifestyles factors and depressive symptoms among the general adult population in Japan. Method Participants were randomly selected from the Japanese general adult population. Data from 2334 people aged 20 years or older were analyzed. This cross-sectional survey was conducted in August and September 2009. Participants completed a face-to-face interview about unhealthy lifestyle factors, including lack of exercise, skipping breakfast, a poorly balanced diet, snacking between meals, insufficient sleep, current smoking, alcohol drinking, and obesity. Presence of depressive symptoms was defined as a score of ≥ 16 on the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D). Relationships between unhealthy lifestyle factors and depressive symptoms were evaluated by multivariate logistic regression analysis adjusting for sociodemographic variables and other unhealthy lifestyle factors. Results Multivariate logistic regression analysis revealed that insufficient sleep, a poorly balanced diet, snacking between meals and lack of exercise were significantly associated with the prevalence of depressive symptoms, with odds ratios ranging from 1.56 for lack of exercise to 3.98 for insufficient sleep. Limitations Since this study was a cross-sectional study, causal relationships could not be determined. Conclusion These results suggest that promoting a healthy lifestyle focused on sleep, food intake and exercise may be important for individuals with depressive symptoms.

Ghazizadeh-Hashemi, M., A. Ghajar, et al. (2018). ***"Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial."*** Journal of Affective Disorders 232: 127-133. http://www.sciencedirect.com/science/article/pii/S0165032717324278

Experimental studies provide evidence for antidepressant effects of Palmitoylethanolamide (PEA) in animal models of depression. We aimed to evaluate the efficacy and tolerability of PEA add-on therapy in treatment of patients with major depressive disorder (MDD). Methods In a randomized double-blind, and placebo-controlled study, 58 patients with MDD (DSM-5) and Hamilton Depression Rating Scale (HAM-D) score ≥ 19 were randomized to receive either 600 mg twice daily Palmitoylethanolamide or placebo in addition to citalopram for six weeks. Patients were assessed using the HAM-D scale at baseline and weeks 2, 4, and 6. Results Fifty-four individuals completed the trial. At week 2, patients in the PEA group demonstrated significantly greater reduction in HAM-D scores compared to the placebo group (8.30 ± 2.41 vs. 5.81 ± 3.57, P = .004). The PEA group also demonstrated significantly greater improvement in depressive symptoms [F (3, 156) = 3.35, P = .021] compared to the placebo group throughout the trial period. The patients in the PEA group experienced more response rate (≥ 50% reduction in the HAM-D score) than the placebo group (100% vs. 74% respectively, P = .01) at the end of the trial. Baseline parameters and frequency of side effects were not significantly different between the two groups. Limitations The population size in this study was small and the follow-up period was relatively short. Conclusions Palmitoylethanolamide adjunctive therapy to citalopram can effectively improve symptoms of patients (predominantly male gender) with major depressive disorder. PEA showed rapid-onset antidepressant effects which need further investigation.

Goetter, E. M., C. M. Mauro, et al. (2018). ***"Treatment expectancy and working alliance in pharmacotherapy as predictors of outcomes in complicated grief."*** Journal of Consulting and Clinical Psychology 86(4): 367-371. http://psycnet.apa.org/record/2018-14401-004

Objective: Nonspecific factors, such as treatment outcome expectancy and working alliance, can influence treatment outcome. No studies to date have examined the role of expectancy and alliance on pharmacotherapy outcomes in individuals with complicated grief (CG). Method: This secondary analysis of a larger randomized, control trial (RCT) examined the relationship between pharmacotherapy expectancy and alliance on treatment outcome in adults with CG who were participating in a multisite, double-blind, RCT examining the efficacy of citalopram and complicated grief treatment (CGT). Participants (n = 202) were randomized to one of four treatment conditions: citalopram (CIT), placebo (PBO), CGT + citalopram (CGT + CIT), or CGT + placebo (CGT + PBO). Results: Pharmacotherapy outcome expectancy and working alliance were higher among individuals randomized to CGT + CIT and CGT + PBO compared with CIT or PBO without CGT. Pharmacotherapy outcome expectancy was higher at Week 2 among individuals who ultimately responded to treatment compared with those who did not and among those who remained in treatment compared with those who dropped out. In contrast, working alliance did not correlate with dropout or treatment outcomes in pharmacotherapy. Conclusions: Expectancy for medication was higher among individuals randomized to receive CGT. Clinicians should assess symptoms and expectancies in the first weeks of treatment because these could be early markers of drop out and treatment response.

Grunebaum, M. F., H. C. Galfalvy, et al. (2018). ***"Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial."*** American Journal of Psychiatry 175(4): 327-335. https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2017.17060647

Objective: Pharmacotherapy to rapidly relieve suicidal ideation in depression may reduce suicide risk. Rapid reduction in suicidal thoughts after ketamine treatment has mostly been studied in patients with low levels of suicidal ideation. The authors tested the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder. Method: In a randomized clinical trial, adults (N=80) with current major depressive disorder and a score ≥4 on the Scale for Suicidal Ideation (SSI), of whom 54% (N=43) were taking antidepressant medication, were randomly assigned to receive ketamine or midazolam infusion. The primary outcome measure was SSI score 24 hours after infusion (at day 1). Results: The reduction in SSI score at day 1 was 4.96 points greater for the ketamine group compared with the midazolam group (95% CI=2.33, 7.59; Cohen's d=0.75). The proportion of responders (defined as having a reduction ≥50% in SSI score) at day 1 was 55% for the ketamine group and 30% for the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; number needed to treat=4.0). Improvement in the Profile of Mood States depression subscale was greater at day 1 for the ketamine group compared with the midazolam group (estimate=7.65, 95% CI=1.36, 13.94), and this effect mediated 33.6% of ketamine's effect on SSI score. Side effects were short-lived, and clinical improvement was maintained for up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up. Conclusions: Adjunctive ketamine demonstrated a greater reduction in clinically significant suicidal ideation in depressed patients within 24 hours compared with midazolam, partially independently of antidepressant effect. [Note too the thoughtful linked editorial in the same issue of this journal].

Hasin, D. S., A. L. Sarvet, et al. (2018). ***"Epidemiology of adult dsm-5 major depressive disorder and its specifiers in the united states."*** JAMA Psychiatry 75(4): 336-346. http://dx.doi.org/10.1001/jamapsychiatry.2017.4602

Importance No US national data are available on the prevalence and correlates of DSM-5–defined major depressive disorder (MDD) or on MDD specifiers as defined in DSM-5.Objective To present current nationally representative findings on the prevalence, correlates, psychiatric comorbidity, functioning, and treatment of DSM-5 MDD and initial information on the prevalence, severity, and treatment of DSM-5 MDD severity, anxious/distressed specifier, and mixed-features specifier, as well as cases that would have been characterized as bereavement in DSM-IV. Design, Setting, and Participants In-person interviews with a representative sample of US noninstitutionalized civilian adults (≥18 years) (n = 36 309) who participated in the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III). Data were collected from April 2012 to June 2013 and were analyzed in 2016-2017. Main Outcomes and Measures Prevalence of DSM-5 MDD and the DSM-5

specifiers. Odds ratios (ORs), adjusted ORs (aORs), and 95% CIs indicated associations with demographic characteristics and other psychiatric disorders.Results Of the 36 309 adult participants in NESARC-III, 12-month and lifetime prevalences of MDD were 10.4% and 20.6%, respectively. Odds of 12-month MDD were significantly lower in men (OR, 0.5; 95% CI, 0.46-0.55) and in African American (OR, 0.6; 95% CI, 0.54-0.68), Asian/Pacific Islander (OR, 0.6; 95% CI, 0.45-0.67), and Hispanic (OR, 0.7; 95% CI, 0.62-0.78) adults than in white adults and were higher in younger adults (age range, 18-29 years; OR, 3.0; 95% CI, 2.48-3.55) and those with low incomes ($19 999 or less; OR, 1.7; 95% CI, 1.49-2.04). Associations of MDD with psychiatric disorders ranged from an aOR of 2.1 (95% CI, 1.84-2.35) for specific phobia to an aOR of 5.7 (95% CI, 4.98-6.50) for generalized anxiety disorder. Associations of MDD with substance use disorders ranged from an aOR of 1.8 (95% CI, 1.63-2.01) for alcohol to an aOR of 3.0 (95% CI, 2.57-3.55) for any drug. Most lifetime MDD cases were moderate (39.7%) or severe (49.5%). Almost 70% with lifetime MDD had some type of treatment. Functioning among those with severe MDD was approximately 1 SD below the national mean. Among 12.9% of those with lifetime MDD, all episodes occurred just after the death of someone close and lasted less than 2 months. The anxious/distressed specifier characterized 74.6% of MDD cases, and the mixed-features specifier characterized 15.5%. Controlling for severity, both specifiers were associated with early onset, poor course and functioning, and suicidality. Conclusions and Relevance Among US adults, DSM-5 MDD is highly prevalent, comorbid, and disabling. While most cases received some treatment, a substantial minority did not. Much remains to be learned about the DSM-5 MDD specifiers in the general population.

Henssler, J., M. Kurschus, et al. (2018). ***"Long-term acute-phase treatment with antidepressants, 8 weeks and beyond: A systematic review and meta-analysis of randomized, placebo-controlled trials."*** J Clin Psychiatry 79(1). https://www.ncbi.nlm.nih.gov/pubmed/28068463

OBJECTIVE: In clinical practice, acute antidepressant treatment is often applied for several months until remission is achieved. However, data on treatment outcomes beyond 8 weeks are sparse and no systematic review exists to date. This study aims at assessing efficacy and tolerability of antidepressants compared to placebo in acute treatment at and beyond 8 weeks. DATA SOURCES: MEDLINE, Embase, PsycINFO, and CENTRAL databases were systematically searched through March 2014 using generic terms for depressive and affective disorders combined with generic terms for individual drugs and placebo. STUDY SELECTION: Double-blind, randomized, placebo-controlled studies of 8 weeks or more comparing antidepressant monotherapy to placebo in adult patients with acute depressive disorder. DATA EXTRACTION: Data extraction and synthesis followed guidelines of the Cochrane Collaboration. All data were extracted independently by 2 reviewers. Primary outcome was standardized mean difference (SMD) between antidepressant and placebo; secondary outcomes were response, remission, and dropouts. RESULTS: Of 6,043 articles screened, we selected 104 studies that met criteria and included 35,052 patients. Active treatment was statistically significantly superior to placebo, with consistent effect sizes (SMD [95% CL]) after 8, 12, 16, 20, and 24 weeks: 0.27 (0.24, 0.30), 0.34 (0.25, 0.43), 0.24 (0.09, 0.40), 0.31 (0.12, 0.51), and 0.34 (0.18, 0.50), respectively. Results remained stable across secondary outcomes and subgroup and sensitivity analyses. CONCLUSIONS: Effect sizes of antidepressant monotherapy compared to placebo seem to be stable over 6 months. These results challenge the assumption that long-term antidepressant effects are due to the natural course of the disorder rather than to a pharmacologic effect.

Henssler, J., M. Kurschus, et al. (2018). ***"Trajectories of acute antidepressant efficacy: How long to wait for response? A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials."*** J Clin Psychiatry 79(3). https://www.ncbi.nlm.nih.gov/pubmed/29659207

BACKGROUND: In patients who are not responding to antidepressant pharmacotherapy, information regarding the future probability of response with the same treatment is scarce. Specifically, it is unclear at what point in time the probability to respond or remit ceases to increase, because few studies report data on response or remission at repeated time points beyond 4 or 8 weeks of treatment. Consequently, treatment recommendations in clinical practice guidelines differ widely. DATA SOURCES: We systematically searched MEDLINE, Embase, PsycINFO, and CENTRAL databases through March 2014 using generic terms for depressive or affective disorders, individual drug names, and placebo (Prospero Registration: CRD42014010105). STUDY SELECTION: We identified double-blind, randomized studies with continuous outcome reporting from 4 weeks up to at least 12 weeks that compared antidepressant monotherapy to placebo in adult patients suffering from acute depressive disorder. DATA EXTRACTION: Data extraction and synthesis followed Cochrane Collaboration guidelines. Primary outcome was response; secondary outcomes were remission and changes in rating scale scores in previously unresponsive patients, respectively. RESULTS: Of 6,043 articles screened, we selected 9 studies including 3,466 patients. Altogether, 21.6% (18.6%, 24.9%) of previously nonresponsive patients achieved response with ongoing antidepressant treatment between weeks 5 and 8, and 9.9% (7.5%, 12.7%), between weeks 9 and 12. Probability of response when taking placebo was 13.0% (9.9%, 16.5%) between weeks 5 and 8 and 2.4% (1.2%, 4.6%) between weeks 9 and 12. Differences in the probability of response between antidepressant and placebo translated into a number needed to treat of 11 after 4 weeks and 17 after 8 weeks. Heterogeneity was low to moderate, and results remained stable across subgroup and sensitivity analyses. CONCLUSIONS: In patients unresponsive to antidepressant pharmacotherapy, improvements in psychopathology can be expected with ongoing antidepressant treatment for up to 3 months. After 8 weeks of treatment, improvement with ongoing monotherapy is relatively small.

Khambadkone, S. G., Z. A. Cordner, et al. (2018). ***"Nitrated meat products are associated with mania in humans and altered behavior and brain gene expression in rats."*** Molecular Psychiatry. https://doi.org/10.1038/s41380-018-0105-6

Mania is a serious neuropsychiatric condition associated with significant morbidity and mortality. Previous studies have suggested that environmental exposures can contribute to mania pathogenesis. We measured dietary exposures in a cohort of individuals with mania and other psychiatric disorders as well as in control individuals without a psychiatric disorder. We found that a history of eating nitrated dry cured meat [bacon, salami, chorizo, bratwurst, etc] but not other meat or fish products was strongly and independently associated with current mania (adjusted odds ratio 3.49, 95% confidence interval (CI) 2.24–5.45, $p < 8.97 \times 10-8$). Lower odds of association were found between eating nitrated dry cured meat and other psychiatric disorders. We further found that the feeding of meat preparations with added nitrate to rats resulted in hyperactivity reminiscent of human mania, alterations in brain pathways that have been implicated in human bipolar disorder, and changes in intestinal microbiota. These findings may lead to new methods for preventing mania and for developing novel therapeutic interventions. [note nitrated meats have already been shown to be significantly carinogenic].

Khandaker, G. M., J. Stochl, et al. (2018). ***"Childhood inflammatory markers and intelligence as predictors of subsequent persistent depressive symptoms: A longitudinal cohort study."*** Psychological Medicine 48(9): 1514-1522. https://www.cambridge.org/core/article/childhood-inflammatory-markers-and-intelligence-as-predictors-of-subsequent-persistent-depressive-symptoms-a-longitudinal-cohort-study/91808445D2FA14DF4E9A6D2A5075C10B

(Available in free full text) Background To identify developmental sub-groups of depressive symptoms during the second decade of life, a critical period of brain development, using data from a prospective birth cohort. To test whether childhood intelligence and inflammatory markers are associated with subsequent persistent depressive symptoms. Methods IQ,

a proxy for neurodevelopment, was measured at age 8 years. Interleukin 6 (IL-6) and C-reactive protein, typical inflammatory markers, were measured at age 9 years. Depressive symptoms were measured six times between 10 and 19 years using the short mood and feelings questionnaire (SMFQ), which were coded as binary variable and then used in latent class analysis to identify developmental sub-groups of depressive symptoms. Results Longitudinal SMFQ data from 9156 participants yielded three distinct population sub-groups of depressive symptoms: no symptoms (81.2%); adolescent-onset symptoms (13.2%); persistent symptoms (5.6%). Lower IQ and higher IL-6 levels in childhood were independently associated with subsequent persistent depressive symptoms in a linear, dose–response fashion, but not with adolescent-onset symptoms. Compared with the group with no symptoms the adjusted odds ratio for persistent depressive symptoms per s.d. increase in IQ was 0.80 (95% CI, 0.68–0.95); that for IL-6 was 1.20 (95% CI, 1.03–1.39). Evidence for an association with IL-6 remained after controlling for initial severity of depressive symptoms at 10 years. There was no evidence that IL-6 moderated or mediated the IQ-persistent depressive symptom relationship. Conclusions The results indicate potentially important roles for two distinct biological processes, neurodevelopment and inflammation, in the aetiology of persistent depressive symptoms in young people.

Lähteenvuo, M., A. Tanskanen, et al. (2018). ***"Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a finnish nationwide cohort of patients with bipolar disorder."*** JAMA Psychiatry 75(4): 347-355. http://dx.doi.org/10.1001/jamapsychiatry.2017.4711

Importance Mood stabilizers and antipsychotics are the main maintenance treatments for bipolar disorder. Lithium is considered to be the most effective mood stabilizer, but very little is known about overall health outcomes associated with specific treatments and the comparative long-term effectiveness of specific psychotropics or routes of administration in the prevention of rehospitalizations.Objective To study the comparative effectiveness of pharmacologic treatments in the prevention of rehospitalization in a nationwide cohort of patients with bipolar disorder.Design, Setting, and Participants This cohort study examined the risk of psychiatric, cardiovascular, and all-cause hospitalization from January 1, 1987, to December 31, 2012, among all patients in Finland who had been hospitalized for bipolar disorder (N = 18 018; mean follow-up time, 7.2 years) using prospectively gathered nationwide databases for hospitalization and dispensed medications. The primary analysis was within-individual analysis, in which each individual was used as his or her own control to eliminate selection bias. The study adjusted for the effect of concomitant psychotropic medications, duration of illness, and the temporal orders of exposure and nonexposure periods. Statistical analysis was conducted from January 1, 1996, to December 31, 2012.Main Outcomes and Measures Adjusted hazard ratios (HRs) for rehospitalization were calculated.Results Among the cohort (9558 women and 8460 men; mean [SD] age, 46.6 [17.0] years), 9721 patients (54.0%) had at least 1 psychiatric rehospitalization. In comparison between use and no use among specific agents reaching nominal statistical significance, risperidone long-acting injection (HR, 0.58 [95% CI, 0.34-1.00]), gabapentin (HR, 0.58 [95% CI, 0.44-0.77]), perphenazine long-acting injection (HR, 0.60 [95% CI, 0.41-0.88]), and lithium carbonate (HR, 0.67 [95% CI, 0.60-0.73]) were associated with the lowest risk of psychiatric rehospitalization. Concerning all-cause hospitalization, lithium (HR, 0.71 [95% CI, 0.66-0.76]) was associated with the lowest risk. The most frequently used antipsychotic treatment, quetiapine fumarate, showed only modest effectiveness (risk of psychiatric rehospitalization: HR, 0.92 [95% CI, 0.85-0.98]; risk of all-cause hospitalization: HR, 0.93 [95% CI, 0.88-0.98]). Long-acting injections were associated with substantially better outcomes compared with identical oral antipsychotics (risk of psychiatric rehospitalization: HR, 0.70 [95% CI, 0.55-0.90]; risk of all-cause hospitalization: HR, 0.70 [95% CI, 0.57-0.86]). Results from sensitivity analyses showed consistent beneficial effects only for lithium and for long-acting injections compared with their oral counterparts.Conclusions and Relevance Lithium was the most effective mood stabilizer, and long-acting injections the most effective antipsychotics, in preventing hospitalization due to mental or physical illness.

Lassale, C., G. D. Batty, et al. (2018). ***"Healthy dietary indices and risk of depressive outcomes: A systematic review and meta-analysis of observational studies."*** Molecular Psychiatry. https://doi.org/10.1038/s41380-018-0237-8

(Available in free full text) With depression being the psychiatric disorder incurring the largest societal costs in developed countries, there is a need to gather evidence on the role of nutrition in depression, to help develop recommendations and guide future psychiatric health care. The aim of this systematic review was to synthesize the link between diet quality, measured using a range of predefined indices, and depressive outcomes. Medline, Embase and PsychInfo were searched up to 31st May 2018 for studies that examined adherence to a healthy diet in relation to depressive symptoms or clinical depression. Where possible, estimates were pooled using random effect meta-analysis with stratification by observational study design and dietary score. A total of 20 longitudinal and 21 cross-sectional studies were included. These studies utilized an array of dietary measures, including: different measures of adherence to the Mediterranean diet, the Healthy Eating Index (HEI) and Alternative HEI (AHEI), the Dietary Approaches to Stop Hypertension, and the Dietary Inflammatory Index. The most compelling evidence was found for the Mediterranean diet and incident depression, with a combined relative risk estimate of highest vs. lowest adherence category from four longitudinal studies of 0.67 (95% CI 0.55–0.82). A lower Dietary Inflammatory Index was also associated with lower depression incidence in four longitudinal studies (relative risk 0.76; 95% CI: 0.63–0.92). There were fewer longitudinal studies using other indices, but they and cross-sectional evidence also suggest an inverse association between healthy diet and depression (e.g., relative risk 0.65; 95% CI 0.50–0.84 for HEI/AHEI). To conclude, adhering to a healthy diet, in particular a traditional Mediterranean diet, or avoiding a pro-inflammatory diet appears to confer some protection against depression in observational studies. This provides a reasonable evidence base to assess the role of dietary interventions to prevent depression.

Lopresti, A. L., P. D. Drummond, et al. (2018). ***"Affron®, a standardised extract from saffron (crocus sativus l.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study."*** Journal of Affective Disorders 232: 349-357. http://www.sciencedirect.com/science/article/pii/S0165032717327131

Background Saffron has antidepressant and anxiolytic effects in adults with mild-to-moderate depression. However, this is the first study examining its mood-related effects in teenagers. Methods In this 8-week, randomised, double-blind, placebo-controlled study, youth aged 12–16 years, with mild-to-moderate anxiety or depressive symptoms were given tablets containing placebo or a saffron extract (affron®, 14 mg b.i.d). The youth and parent versions of the Revised Child Anxiety and Depression Scale (RCADS) were used as outcome measures. Results 80 participants were enrolled and 68 completed the study. Based on youth self-reports, affron® was associated with greater improvements in overall internalising symptoms ($p = 0.049$), separation anxiety ($p = 0.003$), social phobia ($p = 0.023$), and depression ($p = 0.016$). Total internalising scores decreased by an average of 33% compared to 17% in the placebo group ($p = 0.029$). However, parental reports of improvements were inconsistent as mean improvements in RCADS scores were greater in the saffron group (40% vs 26%) ($p = 0.026$), although no other significant differences were identified. affron® was well-tolerated and there was a trend of reduced headaches in participants on the active treatment. Limitations The use of a self-report instrument, limited study duration, single treatment dose, and non-clinical sample used in this study limit the generalisability of study findings. Conclusion The administration of a standardised saffron extract (affron®) for 8 weeks improved anxiety and depressive symptoms in youth with mild-to-moderate symptoms, at least from the perspective of the adolescent. However, these beneficial effects were inconsistently corroborated by parents.

Lyall, L. M., C. A. Wyse, et al. (2018). ***"Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: A cross-sectional study of 91 105 participants from the uk biobank."*** The Lancet Psychiatry. http://dx.doi.org/10.1016/S2215-0366(18)30139-1

Background Disruption of sleep and circadian rhythmicity is a core feature of mood disorders and might be associated with increased susceptibility to such disorders. Previous studies in this area have used subjective reports of activity and sleep patterns, but the availability of accelerometer-based data from UK Biobank participants permits the derivation and analysis of new, objectively ascertained circadian rhythmicity parameters. We examined associations between objectively assessed circadian rhythmicity and mental health and wellbeing phenotypes, including lifetime history of mood disorder. Methods UK residents aged 37–73 years were recruited into the UK Biobank general population cohort from 2006 to 2010. We used data from a subset of participants whose activity levels were recorded by wearing a wrist-worn accelerometer for 7 days. From these data, we derived a circadian relative amplitude variable, which is a measure of the extent to which circadian rhythmicity of rest–activity cycles is disrupted. In the same sample, we examined cross-sectional associations between low relative amplitude and mood disorder, wellbeing, and cognitive variables using a series of regression models. Our final model adjusted for age and season at the time that accelerometry started, sex, ethnic origin, Townsend deprivation score, smoking status, alcohol intake, educational attainment, overall mean acceleration recorded by accelerometry, body-mass index, and a binary measure of childhood trauma. Findings We included 91 105 participants with accelerometery data collected between 2013 and 2015 in our analyses. A one-quintile reduction in relative amplitude was associated with increased risk of lifetime major depressive disorder (odds ratio [OR] 1·06, 95% CI 1·04–1·08) and lifetime bipolar disorder (1·11, 1·03–1·20), as well as with greater mood instability (1·02, 1·01–1·04), higher neuroticism scores (incident rate ratio 1·01, 1·01–1·02), more subjective loneliness (OR 1·09, 1·07–1·11), lower happiness (0·91, 0·90–0·93), lower health satisfaction (0·90, 0·89–0·91), and slower reaction times (linear regression coefficient 1·75, 1·05–2·45). These associations were independent of demographic, lifestyle, education, and overall activity confounders. Interpretation Circadian disruption is reliably associated with various adverse mental health and wellbeing outcomes, including major depressive disorder and bipolar disorder. Lower relative amplitude might be linked to increased susceptibility to mood disorders.

Meesters, Y., W. B. Duijzer, et al. (2018). ***"The effects of low-intensity narrow-band blue-light treatment compared to bright white-light treatment in seasonal affective disorder."*** Journal of Affective Disorders 232: 48-51. http://www.sciencedirect.com/science/article/pii/S0165032717318049

Background Ever since a new photoreceptor was discovered with a highest sensitivity to 470–490 nm blue light, it has been speculated that blue light has some advantages in the treatment of Seasonal Affective Disorder (SAD) over more traditional treatments. In this study we compared the effects of exposure to narrow-band blue light (BLUE) to those of broad-wavelength white light (BLT) in the treatment of SAD. Methods In a 15-day design, 45 patients suffering from SAD completed 30-min sessions of light treatment on 5 consecutive days. 21 subjects received white-light treatment (BLT, broad-wavelength without UV, 10 000 lx, irradiance 31.7 W/m2), 24 subjects received narrow-band blue light (BLUE, 100 lx, irradiance 1.0 W/m2). All participants completed weekly questionnaires concerning mood and energy levels, and were also assessed by means of the SIGH-SAD, which is the primary outcome measure. Results On day 15, SIGH-SAD ratings were significantly lower than on day 1 (BLT 73.2%, effect size 3.37; BLUE 67%, effect size 2.63), which outcomes were not statistically significant different between both conditions. Limitations Small sample size. Conclusions Light treatment is an effective treatment for SAD. The use of narrow-band blue light is equally effective as a treatment using bright white-light.

Morrison, A. P., H. Law, et al. (2018). ***"Antipsychotic drugs versus cognitive behavioural therapy versus a combination of both in people with psychosis: A randomised controlled pilot and feasibility study."*** The Lancet Psychiatry 5(5): 411-423. http://dx.doi.org/10.1016/S2215-0366(18)30096-8

Background Little evidence is available for head-to-head comparisons of psychosocial interventions and pharmacological interventions in psychosis. We aimed to establish whether a randomised controlled trial of cognitive behavioural therapy (CBT) versus antipsychotic drugs versus a combination of both would be feasible in people with psychosis. Methods We did a single-site, single-blind pilot randomised controlled trial in people with psychosis who used services in National Health Service trusts across Greater Manchester, UK. Eligible participants were aged 16 years or older; met ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met the entry criteria for an early intervention for psychosis service; were in contact with mental health services, under the care of a consultant psychiatrist; scored at least 4 on delusions or hallucinations items, or at least 5 on suspiciousness, persecution, or grandiosity items on the Positive and Negative Syndrome Scale (PANSS); had capacity to consent; and were help-seeking. Participants were assigned (1:1:1) to antipsychotics, CBT, or antipsychotics plus CBT. Randomisation was done via a secure web-based randomisation system (Sealed Envelope), with randomised permuted blocks of 4 and 6, stratified by gender and first episode status. CBT incorporated up to 26 sessions over 6 months plus up to four booster sessions. Choice and dose of antipsychotic were at the discretion of the treating consultant. Participants were followed up for 1 year. The primary outcome was feasibility (ie, data about recruitment, retention, and acceptability), and the primary efficacy outcome was the PANSS total score (assessed at baseline, 6, 12, 24, and 52 weeks). Non-neurological side-effects were assessed systemically with the Antipsychotic Non-neurological Side Effects Rating Scale. Primary analyses were done by intention to treat; safety analyses were done on an as-treated basis. The study was prospectively registered with ISRCTN, number ISRCTN06022197. Findings Of 138 patients referred to the study, 75 were recruited and randomly assigned—26 to CBT, 24 to antipsychotics, and 25 to antipsychotics plus CBT. Attrition was low, and retention high, with only four withdrawals across all groups. 40 (78%) of 51 participants allocated to CBT attended six or more sessions. Of the 49 participants randomised to antipsychotics, 11 (22%) were not prescribed a regular antipsychotic. Median duration of total antipsychotic treatment was 44·5 weeks (IQR 26–51). PANSS total score was significantly reduced in the combined intervention group compared with the CBT group (−5·65 [95% CI −10·37 to −0·93]; p=0·019). PANSS total scores did not differ significantly between the combined group and the antipsychotics group (−4·52 [95% CI −9·30 to 0·26]; p=0·064) or between the antipsychotics and CBT groups (−1·13 [95% CI −5·81 to 3·55]; p=0·637). Significantly fewer side-effects, as measured with the Antipsychotic Non-neurological Side Effects Rating Scale, were noted in the CBT group than in the antipsychotics (3·22 [95% CI 0·58 to 5·87]; p=0·017) or antipsychotics plus CBT (3·99 [95% CI 1·36 to 6·64]; p=0·003) groups. Only one serious adverse event was thought to be related to the trial (an overdose of three paracetamol tablets in the CBT group). Interpretation A head-to-head clinical trial of CBT versus antipsychotics versus the combination of the two is feasible and safe in people with first-episode psychosis.

Murrough, J. W., K. M. Huryk, et al. (2018). ***"A pilot study of minocycline for the treatment of bipolar depression: Effects on cortical glutathione and oxidative stress in vivo."*** Journal of Affective Disorders 230: 56-64. http://www.sciencedirect.com/science/article/pii/S0165032717313459

Background The antibiotic minocycline appears to promote neuroprotection through antioxidant and other mechanisms that may be relevant to the pathophysiology of bipolar disorder. The present study assessed the efficacy of minocycline in bipolar depression and examined the association between minocycline treatment and brain glutathione (GSH), an essential

regulator of oxidative stress. Method Twenty patients with bipolar disorder experiencing acute depressive symptoms enrolled in an 8-week, open-label trial of adjuvant minocycline. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and proton magnetic resonance spectroscopy (1H MRS) measures of cortical GSH within a voxel prescribed in the precuneus and aspects of the occipital cortex were obtained from a subset of patients (n=12) before and after treatment. Results The daily dose of minocycline at study end was 256mg (SD: 71mg). Treatment was associated with improvements in depression severity [MADRS score change: −14.6 (95% CI: −7.8 to −21.3)]. Ten patients (50%) were classified as responders based on a ≥50% reduction in MADRS score and 8 patients (40%) were classified as remitters (MADRS score ≤ 9). Higher baseline GSH levels were associated with greater improvement in MADRS score following treatment (ρ=0.51, p=0.05). Increases in GSH levels at study end were higher in non-responders than in responders (p=0.04). Limitations Small sample size, lack of a placebo group. Conclusion Minocycline may be an effective adjuvant treatment for bipolar depression, particularly in patients with high baseline GSH levels. Further research is needed to evaluate the potential of minocycline in this population.

Na, P. J., S. R. Yaramala, et al. (2018). ***"The phq-9 item 9 based screening for suicide risk: A validation study of the patient health questionnaire (phq)−9 item 9 with the columbia suicide severity rating scale (c-ssrs)."*** Journal of Affective Disorders 232: 34-40. http://www.sciencedirect.com/science/article/pii/S0165032717309655

Background Item 9 of the Patient Health Questionnaire (PHQ) evaluates passive thoughts of death or self-injury within the last two weeks, and is often used to screen depressed patients for suicide risk. We aimed to validate the PHQ-9 item 9 with a brief electronic version of the Columbia Suicide Severity Rating Scale (eC-SSRS). Methods We analyzed data from 841 patients enrolled in the National Network of Depression Centers Clinical Care Registry. We performed a validation analysis of PHQ-9 item 9 for suicide risk and ideation, using the eC-SSRS as a gold standard (defined as positive response to suicidal ideation with intent to act or recent suicidal behavior). Results Of the 841 patients, 13.4% and 41.1% were assessed as being positive for suicide risk by the eC-SSRS and PHQ-9 item 9, respectively. For the overall cohort, sensitivity was 87.6% (95%CI 80.2–92.5%), specificity was 66.1% (95%CI 62.6–69.4%), PPV was 28.6% (95%CI 24.1–33.6%), and NPV was 97.2% (95%CI 95.3–98.3%) for the PHQ-9 suicide item. These performance measures varied within subgroups defined by demographic and clinical characteristics. In addition, the validity of PHQ-9 item 9 (cutoff score of 1) with eC-SSRS-defined suicide ideation showed overall poor results. Limitations The gold standard used in our study was a surrogate measure of suicidality based on eC-SSRS scores. Conclusions The results of our study suggest that item 9 of the PHQ-9 is an insufficient assessment tool for suicide risk and suicide ideation, with limited utility in certain demographic and clinical subgroups that requires further investigation.

Nasca, C., B. Bigio, et al. (2018). ***"Acetyl-l-carnitine deficiency in patients with major depressive disorder."*** Proceedings of the National Academy of Sciences. http://www.pnas.org/content/pnas/early/2018/07/24/1801609115.full.pdf

Identifying biological targets in major depressive disorder (MDD) is a critical step for development of effective mechanism-based medications. The epigenetic agent acetyl-l-carnitine (LAC) has rapid and enduring antidepressant-like effects in LAC-deficient rodents. Here, we found that LAC levels were decreased in patients with MDD versus age- and sex-matched healthy controls in two independent study centers. In subsequent exploratory analyses, the degree of LAC deficiency reflected both the severity and age of onset of MDD. Furthermore, the lowest LAC levels were found in patients with treatment-resistant depression, whereby history of emotional neglect and being female predicted decreased LAC levels. These translational findings suggest that LAC may serve as a candidate biomarker to help the diagnosis of a clinical endophenotype of MDD.The lack of biomarkers to identify target populations greatly limits the promise of precision medicine for major depressive disorder (MDD), a primary cause of ill health and disability. The endogenously produced molecule acetyl-l-carnitine (LAC) is critical for hippocampal function and several behavioral domains. In rodents with depressive-like traits, LAC levels are markedly decreased and signal abnormal hippocampal glutamatergic function and dendritic plasticity. LAC supplementation induces rapid and lasting antidepressant-like effects via epigenetic mechanisms of histone acetylation. This mechanistic model led us to evaluate LAC levels in humans. We found that LAC levels, and not those of free carnitine, were decreased in patients with MDD compared with age- and sex-matched healthy controls in two independent study centers. Secondary exploratory analyses showed that the degree of LAC deficiency reflected both the severity and age of onset of MDD. Moreover, these analyses showed that the decrease in LAC was larger in patients with a history of treatment-resistant depression (TRD), among whom childhood trauma and, specifically, a history of emotional neglect and being female, predicted the decreased LAC. These findings suggest that LAC may serve as a candidate biomarker to help diagnose a clinical endophenotype of MDD characterized by decreased LAC, greater severity, and earlier onset as well as a history of childhood trauma in patients with TRD. Together with studies in rodents, these translational findings support further exploration of LAC as a therapeutic target that may help to define individualized treatments in biologically based depression subtype consistent with the spirit of precision medicine.

Pottie, K., W. Thompson, et al. (2018). ***"Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline."*** Evidence-based clinical practice guideline 64(5): 339-351. http://www.cfp.ca/content/cfp/64/5/339.full.pdf

(Available in free full text) Objective To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop benzodiazepine receptor agonists (BZRAs); to focus on the highest level of evidence available and seek input from primary care professionals in the guideline development, review, and endorsement processes. Methods The overall team comprised 8 clinicians (1 family physician, 2 psychiatrists, 1 clinical psychologist, 1 clinical pharmacologist, 2 clinical pharmacists, and 1 geriatrician) and a methodologist; members disclosed conflicts of interest. For guideline development, a systematic process was used, including the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Evidence was generated by conducting a systematic review of BZRA deprescribing trials for insomnia, as well as performing a review of reviews of the harms of continued BZRA use and narrative syntheses of patient preferences and resource implications. This evidence and GRADE quality of evidence ratings were used to generate recommendations. The team refined guideline content and recommendations through consensus and synthesized clinical considerations to address front-line clinician questions. The draft guideline was reviewed by clinicians and stakeholders. Recommendations We recommend that deprescribing (tapering slowly) of BZRAs be offered to elderly adults (≥ 65 years) who take BZRAs, regardless of duration of use, and suggest that deprescribing (tapering slowly) be offered to adults aged 18 to 64 who have used BZRAs for more than 4 weeks. These recommendations apply to patients who use BZRAs to treat insomnia on its own (primary insomnia) or comorbid insomnia where potential underlying comorbidities are effectively managed. This guideline does not apply to those with other sleep disorders or untreated anxiety, depression, or other physical or mental health conditions that might be causing or aggravating insomnia. Conclusion Benzodiazepine receptor agonists are associated with harms, and therapeutic effects might be short term. Tapering BZRAs improves cessation rates compared with usual care without serious harms. Patients might be more amenable to deprescribing conversations if they understand the rationale (potential for harm), are involved in developing the tapering plan, and are offered behavioural advice. This guideline provides recommendations for making decisions about when and how to reduce and stop BZRAs. Recommendations are meant to assist with, not dictate, decision making in conjunction with patients.

Rink, L., C. Braun, et al. (2018). ***"Dose increase versus unchanged continuation of antidepressants after initial antidepressant treatment failure in patients with major depressive disorder: A systematic review and meta-analysis of randomized, double-blind trials."*** J Clin Psychiatry 79(3). https://www.ncbi.nlm.nih.gov/pubmed/29873954

OBJECTIVE: To evaluate the efficacy and tolerability of dose increase compared to dose continuation of the initially prescribed antidepressant in antidepressant treatment failure (ATF). DATA SOURCES: We searched CENTRAL, PubMed, Embase, and PsycINFO using generic terms for depression, dose increase, and randomized controlled trials (RCTs), without date or language restrictions. STUDY SELECTION: Of 1,780 studies screened, 9 studies reporting on 1,273 patients were included for meta-analysis (PROSPERO Registration: CRD42017058389). Studies met the following predetermined inclusion criteria: randomized controlled trial, patients diagnosed with unipolar depression according to a standardized diagnostic instrument, ATF after a standard antidepressant trial (duration of >/= 3 weeks at a standard dose), dose increase regimen, and control group of dose continuation. DATA EXTRACTION: Two authors extracted data independently according to the Cochrane Handbook for Systematic Reviews. Analyses are based on random effects models. RESULTS: All studies reported on selective serotonin reuptake inhibitors (SSRIs); 1 study also reported on maprotiline. Meta-analyses resulted in a statistically nonsignificant summary effect size of 0.053 standardized mean difference (95% CI, -0.143 to 0.248) in favor of antidepressant dose increase. Subgroup and sensitivity analyses and secondary outcome analyses resulted in similar effect estimates and supported the robustness of the results. CONCLUSIONS: With clinically and statistically nonsignificant effect estimates, there is evidence from RCTs against increasing the dose of SSRIs (with the possible exception of citalopram) in adult patients with major depression and ATF. Dose increase with other antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors) and in other patient groups (minor depression, children and adolescents) or after long periods of first-line antidepressant therapy (ie, 8 weeks) have not been or not been sufficiently studied and, at this time, cannot be recommended in clinical practice.

Schuch, F. B., D. Vancampfort, et al. (2018). ***"Physical activity and incident depression: A meta-analysis of prospective cohort studies."*** Am J Psychiatry 175(7): 631-648. https://doi.org/10.1176/appi.ajp.2018.17111194

OBJECTIVE: The authors examined the prospective relationship between physical activity and incident depression and explored potential moderators. METHOD: Prospective cohort studies evaluating incident depression were searched from database inception through Oct. 18, 2017, on PubMed, PsycINFO, Embase, and SPORTDiscus. Demographic and clinical data, data on physical activity and depression assessments, and odds ratios, relative risks, and hazard ratios with 95% confidence intervals were extracted. Random-effects meta-analyses were conducted, and the potential sources of heterogeneity were explored. Methodological quality was assessed using the Newcastle-Ottawa Scale. RESULTS: A total of 49 unique prospective studies (N=266,939; median proportion of males across studies, 47%) were followed up for 1,837,794 person-years. Compared with people with low levels of physical activity, those with high levels had lower odds of developing depression (adjusted odds ratio=0.83, 95% CI=0.79, 0.88; I(2)=0.00). Furthermore, physical activity had a protective effect against the emergence of depression in youths (adjusted odds ratio=0.90, 95% CI=0.83, 0.98), in adults (adjusted odds ratio=0.78, 95% CI=0.70, 0.87), and in elderly persons (adjusted odds ratio=0.79, 95% CI=0.72, 0.86). Protective effects against depression were found across geographical regions, with adjusted odds ratios ranging from 0.65 to 0.84 in Asia, Europe, North America, and Oceania, and against increased incidence of positive screen for depressive symptoms (adjusted odds ratio=0.84, 95% CI=0.79, 0.89) or major depression diagnosis (adjusted odds ratio=0.86, 95% CI=0.75, 0.98). No moderators were identified. Results were consistent for unadjusted odds ratios and for adjusted and unadjusted relative risks/hazard ratios. Overall study quality was moderate to high (Newcastle-Ottawa Scale score, 6.3). Although significant publication bias was found, adjusting for this did not change the magnitude of the associations. CONCLUSIONS: Available evidence supports the notion that physical activity can confer protection against the emergence of depression regardless of age and geographical region.

Swartz, H. A., P. Rucci, et al. (2018). ***"Psychotherapy alone and combined with medication as treatments for bipolar ii depression: A randomized controlled trial."*** J Clin Psychiatry 79(2). https://www.ncbi.nlm.nih.gov/pubmed/28703949

OBJECTIVE: Bipolar II disorder (BP-II) is associated with marked morbidity and mortality. Quetiapine, the treatment with greatest evidence for efficacy in BP-II depression, is associated with metabolic burden. Psychotherapy, a treatment with few side effects, has not been systematically evaluated in BP-II. This study compared psychotherapy plus placebo to psychotherapy plus pharmacotherapy as treatments for BP-II depression. METHODS: From 2010 to 2015, unmedicated adults (n = 92) with DSM-IV-TR BP-II depression were randomly assigned to weekly sessions of Interpersonal and Social Rhythm Therapy (IPSRT) plus placebo or IPSRT plus quetiapine and followed for 20 weeks. RESULTS: For primary outcomes, IPSRT + quetiapine yielded significantly faster improvement on 17-item Hamilton Depression Rating Scale (F(1),(1)(1)(5).(4) = 3.924, P = .048) and greater improvement on Young Mania Rating Scale (F(5)(8).(5) = 4.242, P = .044) scores. Both groups, however, improved significantly over time with comparable response rates (>/= 50% reduction in depression scores): 67.4% (62/92) in the entire sample, with no between-group differences. Those randomly assigned to their preferred treatment were 4.5 times more likely to respond (OR = 4.48, 95% CI = 1.20-16.77, P = .026). IPSRT + quetiapine assignment was associated with significantly higher body mass index over time (F(6)(7).(9)(6) = 6.671, P = .012) and rates of dry mouth (79% v. 58%; chi(2) = 4.0, P = .046) and a trend toward more complaints of oversedation (100% vs 92%; chi(2) = 3.4, P = .063). CONCLUSIONS: IPSRT plus quetiapine resulted in greater symptomatic improvement but also more side effects than IPSRT alone. A subset of participants improved with IPSRT alone, although absence of an inactive comparator limits interpretation of this finding. Receipt of preferred treatment was associated with better outcomes. Harms, benefits, and preferences should be considered when recommending treatments for BP-II depression.

Veronese, N., B. Stubbs, et al. (2018). ***"Acetyl-l-carnitine supplementation and the treatment of depressive symptoms: A systematic review and meta-analysis."*** Psychosomatic Medicine 80(2): 154-159. https://journals.lww.com/psychosomaticmedicine/Fulltext/2018/02000/Acetyl_L_Carnitine_Supplementation_and_the.4.aspx

Objective Deficiency of acetyl-L-carnitine (ALC) seems to play a role in the risk of developing depression, indicating a dysregulation of fatty acid transport across the inner membrane of mitochondria. However, data about ALC supplementation in humans are limited. We thus conducted a systematic review and meta-analysis investigating the effect of ALC on depressive symptoms across randomized controlled trials (RCTs). Methods A literature search in major databases, without language restriction, was undertaken from inception until 30 December 2016. Eligible studies were RCTs of ALC alone or in combination with antidepressant medications, with a control group taking placebo/no intervention or antidepressants. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used for summarizing outcomes with a random-effect model. Results Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants (mean age = 54 years, % female = 65%) were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that ALC significantly reduced depressive symptoms (SMD = −1.10, 95% CI = −1.65 to −0.56, I2 = 86%). In three RCTs comparing ALC versus antidepressants (162 for each group), ALC demonstrated similar effectiveness compared with established antidepressants in reducing depressive symptoms (SMD = 0.06, 95% CI = −0.22 to 0.34, I2 = 31%). In these latter RCTs, the incidence of adverse effects was significantly lower in the ALC group than in the antidepressant

group. Subgroup analyses suggested that ALC was most efficacious in older adults. Conclusions ALC supplementation significantly decreases depressive symptoms compared with placebo/no intervention, while offering a comparable effect with that of established antidepressant agents with fewer adverse effects. Future large scale trials are required to confirm/refute these findings.

Wang, P.-W., H.-C. Lin, et al. (2018). ***"Effect of aerobic exercise on improving symptoms of individuals with schizophrenia: A single blinded randomized control study."*** Frontiers in Psychiatry 9(167). https://www.frontiersin.org/article/10.3389/fpsyt.2018.00167

(Available in free full text) Introduction Antipsychotic treatment can improve the symptoms of schizophrenia; however, residual symptoms after antipsychotic treatment are frequent. The effects of exercise on the symptoms of schizophrenic patients under antipsychotic treatment are not conclusive. The aim of this randomized case–control study was to examine the effects of aerobic exercise (AE) on the symptoms of schizophrenic patients receiving antipsychotic treatment. Method In total, 33 and 29 participants who received antipsychotics for schizophrenia were randomly assigned into intervention and control groups, respectively. We measured the severities of schizophrenic symptoms using the Chinese version of the Positive and Negative Syndrome Scale (PANSS) before, immediately after, and at 3 months after the intervention in both the AE and control groups. Results In total, 24 participants (72.7%) in the AE group and 22 participants (75.9%) in the control group completed the study. The results indicated that the severities of positive symptoms and general psychopathology in the AE group significantly decreased during the 12 weeks of intervention but did not further significantly change during the follow-up period of 3 months. The severity of negative symptoms in the AE group significantly decreased after 12 weeks of intervention and continued decreasing during the 3-month follow-up period. Interaction effects between time and group for the severities of symptoms on the negative and general psychopathology scales were observed. Conclusion AE can improve the severities of symptoms on the negative and general psychopathology scales in individuals with antipsychotic-treated schizophrenia.

Weinberger, A. H., M. Gbedemah, et al. (2018). ***"Trends in depression prevalence in the USA from 2005 to 2015: Widening disparities in vulnerable groups."*** Psychological Medicine 48(8): 1308-1315. https://www.cambridge.org/core/article/trends-in-depression-prevalence-in-the-usa-from-2005-to-2015-widening-disparities-in-vulnerable-groups/8A2904A85BB1F4436102DB78E3854E35

BackgroundMajor depression is associated with significant disability, morbidity, and mortality. The current study estimated trends in the prevalence of major depression in the US population from 2005 to 2015 overall and by demographic subgroups.MethodsData were drawn from the National Survey on Drug Use and Health (NSDUH), an annual cross-sectional study of US persons ages 12 and over (total analytic sample N = 607 520). Past-year depression prevalence was examined annually among respondents from 2005 to 2015. Time trends in depression prevalence stratified by survey year were tested using logistic regression. Data were re-analyzed stratified by age, gender, race/ethnicity, income, and education.ResultsDepression prevalence increased significantly in the USA from 2005 to 2015, before and after controlling for demographics. Increases in depression were significant for the youngest and oldest age groups, men, and women, Non-Hispanic White persons, the lowest income group, and the highest education and income groups. A significant year × demographic interaction was found for age. The rate of increase in depression was significantly more rapid among youth relative to all older age groups.ConclusionsThe prevalence of depression increased significantly in the USA from 2005 to 2015. The rate of increase in depression among youth was significantly more rapid relative to older groups. Further research into understanding the macro level, micro level, and individual factors that are contributing to the increase in depression, including factors specific to demographic subgroups, would help to direct public health prevention and intervention efforts.

Willem van Dalen, J., L. L. van Wanrooij, et al. (2018). ***"Association of apathy with risk of incident dementia: A systematic review and meta-analysis."*** JAMA Psychiatry. http://dx.doi.org/10.1001/jamapsychiatry.2018.1877

Importance Fear of dementia is pervasive in older people with cognitive concerns. Much research is devoted to finding prognostic markers for dementia risk. Studies suggest apathy in older people may be prodromal to dementia and could be a relevant, easily measurable predictor of increased dementia risk. However, evidence is fragmented and methods vary greatly between studies. Objective To systematically review and quantitatively synthesize the evidence for an association between apathy in dementia-free older individuals and incident dementia. Data Sources Two reviewers conducted a systematic search of Medline, Embase, and PsychINFO databases.Study Selection Inclusion criteria were (1) prospective cohort studies, (2) in general populations or memory clinic patients without dementia, (3) with clear definitions of apathy and dementia, and (4) reporting on the association between apathy and incident dementia.Data Extraction and Synthesis PRISMA and MOOSE guidelines were followed. Data were extracted by 1 reviewer and checked by a second. Main Outcomes and Measures Main outcomes were pooled crude risk ratios, maximally adjusted reported hazard ratios (HR), and odds ratios (OR) using DerSimonian-Laird random effects models.Results The mean age of the study populations ranged from 69.2 to 81.9 years (median, 71.6 years) and the percentage of women ranged from 35% to 70% (median, 53%). After screening 2031 titles and abstracts, 16 studies comprising 7365 participants were included. Apathy status was available for 7299 participants. Studies included populations with subjective cognitive concerns (n = 2), mild cognitive impairment (n = 11), cognitive impairment no dementia (n = 1), or mixed cognitive and no cognitive impairment (n = 2). Apathy was present in 1470 of 7299 participants (20.1%). Follow-up ranged from 1.2 to 5.4 years. In studies using validated apathy definitions (n = 12), the combined risk ratio of dementia for patients with apathy was 1.81 (95% CI, 1.32-2.50; I2 = 76%; n = 12), the hazard ratio was 2.39 (95% CI, 1.27-4.51; I2 = 90%; n = 7), and the odds ratio was 17.14 (95% CI, 1.91-154.0; I2 = 60%; n = 2). Subgroup analyses, meta-regression, and individual study results suggested the association between apathy and dementia weakened with increasing follow-up time, age, and cognitive impairment. Meta-regression adjusting for apathy definition and follow-up time explained 95% of heterogeneity in mild cognitive impairment. Conclusions and Relevance Apathy was associated with an approximately 2-fold increased risk of dementia in memory clinic patients. Moderate publication bias may have inflated some of these estimates. Apathy deserves more attention as a relevant, cheap, noninvasive, and easily measureable marker of increased risk of incident dementia with high clinical relevance, particularly because these vulnerable patients may forgo health care.

Wilson, D. M., J. Cohen, et al. (2018). ***"Bereavement grief: A population-based foundational evidence study."*** Death Studies 42(7): 463-469. https://doi.org/10.1080/07481187.2017.1382609

Information is needed on the incidence and prevalence of bereavement grief, and factors associated with severe or prolonged grief. Among 1,208 representative Canadian adults, 96% had experienced bereavement grief and 78% were actively grieving at interview. Grief levels were higher among women, Protestants, and Catholics, when the death was under 2 years previously, when a spouse, parent, or child had died, and when the perceived death quality was lower. This study reveals the importance of good deaths; they are essential for dying people and also those who mourn their deaths.

Yu, J., H.-Y. Lim, et al. (2018). ***"Directional associations between memory impairment and depressive symptoms: Data from a longitudinal sample and meta-analysis."*** Psychological Medicine 48(10): 1664-1672.

https://www.cambridge.org/core/article/directional-associations-between-memory-impairment-and-depressive-symptoms-data-from-a-longitudinal-sample-and-metaanalysis/EAC451D81B174A8A263C12D4B9ED395F

Background Previous cross-lagged studies on depression and memory impairment among the elderly have revealed conflicting findings relating to the direction of influence between depression and memory impairment. The current study aims to clarify this direction of influence by examining the cross-lagged relationships between memory impairment and depression in an Asian sample of elderly community dwellers, as well as synthesizing previous relevant cross-lagged findings via a meta-analysis. Methods A total of 160 participants (Mage = 68.14, s.d. = 5.34) were assessed across two time points (average of 1.9 years apart) on measures of memory and depressive symptoms. The data were then fitted to a structural equation model to examine two cross-lagged effects (i.e. depressive symptoms→memory; memory→depressive symptoms). A total of 14 effect-sizes for each of the two cross-lagged directions were extracted from six studies (including the present; total N = 8324). These effects were then meta-analyzed using a three-level mixed effects model. Results In the current sample, lower memory ability at baseline was associated with worse depressive symptoms levels at follow-up, after controlling for baseline depressive symptoms. However, the reverse effect was not significant; baseline depressive symptoms did not predict subsequent memory ability after controlling for baseline memory. The results of the meta-analysis revealed the same pattern of relationship between memory and depressive symptoms. Conclusions These results provide robust evidence that the relationship between memory impairment and depressive symptoms is unidirectional; memory impairment predicts subsequent depressive symptoms but not vice-versa. The implications of these findings are discussed

Zhao, X., J. Ma, et al. (2018). ***"Light therapy for older patients with non-seasonal depression: A systematic review and meta-analysis."*** Journal of Affective Disorders 232: 291-299.
http://www.sciencedirect.com/science/article/pii/S0165032717314581

Background Light therapy has become an increasingly common treatment for adults with depression, yet the role of light therapy for non-seasonal depression among older adults remains unclear. Objective This meta-analysis sought to evaluate the effectiveness of light therapy among older patients with non-seasonal depression. Methods We searched the Cochrane Central Register of Controlled Trials, PubMed, Embase, Web of Science, CNKI and CBM from the inception of each database to May 2017. Two researchers conducted the literature screening, data extraction, and methodological quality assessment independently. We used the Cochrane Collaboration's bias assessment tool to evaluate the risk of bias for included studies, and Review Manager 5.2.3 Software for the meta-analysis. Results Six trials with a total of 359 patients were included, and five studies were assessed as being of low risk for bias. We evaluated the effect of light therapy on depression by the reduction of depressive symptoms (SMD = 0.45; 95% CI= [0.14, 0.75]). The subgroup analysis did not find significant moderating effects of depression with intervention intensity, light type, measuring scale or intervention duration. Limitations Most of the study samples were not representative of the larger population of adults and therefore caution should be used when interpreting the findings. Conclusions Light therapy has a positive effect on geriatric non-seasonal depression. Studies with larger sample sizes are needed to confirm the curative effect of light therapy in the future.