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Lithium in Chronic Kidney Disease

In a population-based cohort study, continued use of lithium after a diagnosis of mild chronic kidney disease (CKD) did not increase the rate of progression to end-stage renal disease. In addition, switching patients to an anticonvulsant did not confer any protection against kidney failure.

Methods: Data were collected from linked Danish nationwide medical and vital records databases. The study cohort consisted of all patients who received a diagnosis of CKD between 1995 and 2012 who also had a history of lithium or anticonvulsant use during this period. CKD was defined broadly as either definite or possible disease, not requiring dialysis or transplantation. Study outcomes were progression to end-stage renal disease or death. Outcomes were compared in separate cohorts of patients with a history of lithium use or anticonvulsant use. The indication for prescription of these agents was not available, but separate analyses were carried out in subcohorts of patients with a diagnosis of bipolar disorder.

Results: A total of 754 patients received a diagnosis of CKD and were exposed to lithium, including 238 with a bipolar-disorder diagnosis. The anticonvulsant cohort consisted of 5004 patients, of whom 199 had bipolar disorder. The median age of each cohort was 66 years.

Among patients with a history of lithium treatment, about one third continued to use lithium after the diagnosis of CKD, including 32% of those treated for bipolar disorder. In the cohort who continued anticonvulsants after the diagnosis of CKD, 70% of those with bipolar disorder continued anticonvulsants and 21% added on or were switched to lithium.

The absolute risk of progression to end-stage renal disease was 20% over the 10 years post diagnosis, with little difference between patients with lithium or anticonvulsant exposure. Rates of progression to renal failure were decreased by about half in patients who continued taking lithium or anticonvulsants compared with those who discontinued (see table, next page), although the decreased risk was not statistically significant in patients with bipolar disorder receiving anticonvulsants. Risk of the combined outcome of renal failure and death was

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lowered by a similar proportion. For both lithium and anticonvulsants, relative risk of renal failure decreased as the number of prescriptions increased.

Adjusted hazard ratios* for end-stage CKD (ESKD) and death		
Outcome	**All with CKD**	**Bipolar disorder and CKD**
Patients with continued lithium exposure		
ESKD	0.58	0.40
ESKD or death	0.57	0.50
Patients with continued anticonvulsant exposure		
ESKD	0.53	0.70
ESKD or death	0.55	0.50

Discussion: Concerns have been raised that long-term lithium treatment can impair renal function, but modern treatment within recommended serum levels may have eliminated the risk of end-stage renal disease. The present results, while encouraging, require confirmation because it is likely that at least part of the association between medication and reduced end-stage renal disease was the result of bias toward switching medications in patients with more severe kidney disease.

Kessing L, Feldt-Rasmussen B, Andersen P, Gerds T, et al: Continuation of lithium after a diagnosis of chronic kidney disease. *Acta Psychiatrica Scandinavica* 2017;136 (December):615–622. From the University of Copenhagen, Denmark; and other institutions. **Funded by Aalborg University Hospital, Denmark. Three of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Discontinuing Antipsychotics After First Episode

In patients with first-episode psychosis who experienced a full response to medication, early discontinuation of maintenance therapy was associated with poor clinical outcomes at 10 years.[1]

Methods: This follow-up study was conducted in patients who had received treatment for first-episode schizophrenia in a randomized maintenance trial.[2] Patients were aged ≥18 years at initial study entry, had received antipsychotic medication for ≥1 year before enrollment, were free of positive symptoms, and had no history of relapse. Among the exclusion criteria were treatment with clozapine, poor medication adherence, and risk of suicide. At the outset of the trial, patients were randomly assigned to early discontinuation with placebo or maintenance with 400 mg/day quetiapine. The present report describes outcomes in this patient cohort after 10 years of follow-up. Patients had received an average of about 2 years of maintenance treatment before enrollment in the trial and 1 year of treatment during the trial. After the acute trial, patients received naturalistic treatment from non-study physicians and were recontacted after 10 years. The primary outcome of the follow-up study was a composite of positive symptoms or treatment with clozapine at the 10-year evaluation, and suicide. Poor long-term outcome was defined as persistent positive symptoms, requirement for clozapine treatment, or death by suicide.

Results: Charts were reviewed for all 178 patients who participated in the randomized trial, and 142 patients were interviewed during follow-up. All 178 patients were included in the 10-year analysis. Patients received antipsychotics for a mean of nearly 9 of those years. Patients in the placebo group had a higher rate of relapse during the first year after randomization than those receiving maintenance therapy, as previously reported (79% vs 41%; $p<0.0001$). During the 10-year follow-up period, poor long-term outcomes occurred in 39% of patients in the discontinuation group, compared with 21% of the maintenance group (relative risk,* 1.84; $p=0.012$). A mediation analysis showed that relapse during the first year was a significant predictor of poor long-term outcome, accounting for 58% of the difference between the 2 groups.

Discussion: Absent reliable evidence, clinical guidelines recommend antipsychotic maintenance therapy for 12–24 months, with ambivalent recommendations for longer treatment. The present study suggests that for patients who have had a full response, continuing antipsychotic medication for at least the first 3 years after starting treatment may prevent relapse and reduce the risk of a poor outcome.

[1]Hui C, Honer W, Lee E, Chang W, et al: Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30090-7. From the University of Hong Kong, China; and other institutions. **Funded by the Research Grants Council of Hong Kong; and other sources including AstraZeneca. Three of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Chen E, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *British Medical Journal* 2010; doi 10.1136/bmj.c4024.

Common Drug Trade Names*: clozapine—*Clozaril*; quetiapine—*Seroquel

***See Reference Guide.**

Antipsychotics and Venous Thromboembolism

According to a review of observational studies, antipsychotics are likely associated with increased risk of venous thromboembolism (VTE). There are no well-documented differences between first- and second-generation agents or between individual drugs.

VTE encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). Uncontrolled observational studies identified a high incidence of PE in patients with schizophrenia as early as the 1950s, but the association was not widely acknowledged. Following reports of PE and VTE in patients taking clozapine (*Clozaril*) in the 1990s, numerous case–control and cohort studies and meta-analyses were carried out to investigate whether risk was associated with aspects of underlying psychosis, lifestyle factors, or antipsychotic treatment.

A literature review identified 27 observational studies examining the risk of VTE in antipsychotic-treated patients. Although results of some studies were inconclusive, the general direction of this research has been to support an association. Risk estimates are based on heterogeneous studies with different methods, populations, and drug-use patterns. Overall, odds ratios* for VTE ranged from as low as 0.7 to >24. (See table.) It should be noted that most of the evidence comes from case-control studies (n=15), which may overestimate risks. Additional cohort studies are needed to confirm these observations.

Range of odds ratios for VTE in antipsychotic-treated patients	
All antipsychotics	1.1–13.3
First-generation agents	0.89–7.1
Low-potency first-generation agents	0.7–24.1
High-potency first-generation agents	1.5–3.3
Second-generation agents	0.9–3.4
New antipsychotic use	2.0–3.3
Current vs past antipsychotic use	2.0–3.5

The highest risk of antipsychotic-associated VTE occurs during the first 3 months of drug use. Studies comparing risk in users of first- and second-generation agents have not had conclusive results. Although some larger studies of individual agents have been carried out, no agents have been identified with higher or lower risk of VTE than others.

The etiology of antipsychotic-associated VTE is not known and is likely to be multifactorial. Drug-related factors include adverse effects such as sedation, weight gain, and hyperprolactinemia. Obesity and sedentary lifestyle are relatively common in patients with schizophrenia and aggravate risk. Physical restraints can also increase the risk of VTE. Risk for VTE can be estimated using a score that incorporates established nonpsychiatric risk factors such as age, obesity, hormone therapy, dehydration, immobilization, acute infection, and history of DVT

or PE. Risk should be re-evaluated when the clinical situation changes—e.g., infections, surgery, or reduced mobility. Preventive measures include reducing modifiable risk factors and starting prophylactic antithrombotic treatment in hospitalized patients with reduced mobility.

Jonsson A, Schill J, Olsson H, Spigset O, et al: Venous thromboembolism during treatment with antipsychotics: a review of current evidence. *CNS Drugs* 2018;32 (January):47–64. From Linkoping University, Sweden. **This review was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Adjunctive Cannabidiol in Schizophrenia

In a preliminary placebo-controlled trial, adjunctive cannabidiol improved psychotic symptoms and clinical status in patients with schizophrenia.

Background: Cannabidiol (CBD) is 1 of the 2 major components of *Cannabis sativa*. Preliminary research has suggested that it may have antipsychotic properties, and because it acts via a different mechanism than antipsychotics, it may be a promising adjunctive treatment for schizophrenia.

Methods: The present study used a standardized, oral liquid formulation of CBD. The study, conducted at 3 centers in Europe, enrolled adult patients with schizophrenia or a related disorder who had at least a partial response to antipsychotic medication but continued to have a Positive and Negative Syndrome Scale (PANSS) score of ≥60 despite a stable antipsychotic dose for ≥4 weeks. Substance use was not an exclusion criterion. However, patients in whom psychosis may have been induced by substance use were excluded. Participants were randomly assigned to double-blind adjunctive treatment with 1000 mg/day CBD, taken in 2 divided doses, or placebo for 6 weeks. Baseline antipsychotic therapy was continued without change through the study period. Because this was an exploratory study, a number of key endpoints—symptom severity, cognitive performance, and level of functioning—were defined, rather than a single primary outcome.

Results: Of 88 participants (mean age, 41 years; 58% male) enrolled in the trial, 2 discontinued because of adverse events and 3 left the study for other reasons. In the remaining 83 participants, PANSS positive symptom scores (baseline mean, 18 in both groups) were decreased to a significantly greater degree with CBD (mean difference, 1.4 points; p=0.019). The groups did not differ significantly in changes on the PANSS total, negative, or general symptom subscales, or on the Scale for the Assessment of Negative Symptoms, although numeric differences generally favored CBD. Clinical Global Impression–Improvement (CGI-I) ratings showed greater gains in the CBD group, with 78.6% rated by their clinicians as "improved" or better, compared with 54.6% of the placebo group (p=0.018). The proportion of patients rated with mild, borderline, or no illness according to the CGI–Severity scale increased from 16.7% to 45.2% in the CBD group and from 20.5% to 36.4% in the placebo group (p=0.044). Cognitive testing (using the Brief Assessment of Cognition in Schizophrenia (BACS) showed a significantly greater improvement in motor speed in the CBD group than the placebo group (p<0.05). BACS scores for overall cognitive function and executive function favored CBD but the differences were not statistically significant. The difference in scores on the Global Assessment of Functioning scale, while favoring CBD, also did not reach statistical significance.

There were no significant changes in weight, prolactin levels, abnormal movements, or sleep quantity or quality in either group. Adverse events, mostly gastrointestinal, were mild and resolved without treatment.

Discussion: Although the effects of CBD seemed modest, they were achieved with good tolerability and on top of ongoing antipsychotic treatment. The changes in CGI ratings indicate that

CBD-related improvement was apparent to clinicians and therefore probably clinically meaningful. The trend for cognitive improvement raises the possibility that CBD may have positive effects on cognition. The mechanism by which CBD improves psychotic symptoms is unclear, but it does not act via dopamine receptor antagonism like currently available antipsychotic drugs.

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

McGuire P, Robson P, Cubala W, Vasile D, et al: Cannabidiol (CBD) as adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *American Journal of Psychiatry* 2018;175 (March):225–231. From Kings College London, U.K.; and other institutions. **Funded by GW Research Ltd.; and other sources. Six of 8 study authors disclosed financial relationships with commercial sources including GW Research Ltd; the remaining authors declared no competing interests.**

***See Reference Guide.**

Psilocybin in Resistant Depression

In a small, open-label study, administration of psilocybin with psychological support was well tolerated and had long-term beneficial effects in patients with treatment-resistant depression.

Background: Psilocybin is a naturally occurring plant alkaloid that is being increasingly evaluated as treatment for a range of psychiatric disorders including depression. Like other serotonergic psychedelics, psilocybin effects are driven by serotonin 2A receptor activity.

Methods: Study participants (n=20) had unipolar depression of at least moderate severity, with scores of ≥16 on the 21-item Hamilton Rating Scale for Depression (HAM-D), despite receiving ≥2 courses of pharmacologically distinct antidepressants for ≥6 weeks each during the current episode. Following a washout of previous antidepressant therapy, all patients received 2 treatments with psilocybin, first 10 mg and then 25 mg, separated by 1 week. Psychological support began with an introductory preparation visit, in which the therapist built a relationship with the patient and provided information on what to expect. Patients also received emotional support before, during, and after the psilocybin sessions and a follow-up debriefing visit that could include interpretation and advice about maintaining positive changes in outlook and lifestyle. The primary efficacy outcome measure was change from baseline on the self-reported Quick Inventory of Depressive Symptomatology (QIDS-SR), collected 1–3 weeks, 5 weeks, and 3 and 6 months after the high-dose psilocybin session. The psilocybin experience was evaluated using an 11-dimension altered states of consciousness questionnaire.

Results: Of the 20 participants (age range, 27–64 years; 6 women), depression was severe in 18 and moderate in 2. The mean lifetime number of previous treatment trials was 4.6, and 7 patients had previously tried psilocybin. None of these factors was predictive of treatment response.

Outcomes were analyzed for the 19 patients who completed both treatments and all assessments. The average QIDS-SR score was near 20 at study entry and was significantly reduced at all post-treatment time points, with the maximum effect at 5 weeks (9.2-point mean reduction; $p<0.001$; effect size,* 2.3). All 19 patients had reduced QIDS-SR scores beginning 1 week after treatment, and most had sustained improvement at 3–5 weeks. These results were supported by significant reductions in HAM-D and Beck Depression Inventory scores (effect sizes at 1 week, 2.3 and 2.5, respectively; $p<0.0001$ for both). At 6 months, the mean QIDS-SR score was still significantly lower than baseline ($p=0.0035$). Of the 19 patients who completed the study, 5 obtained additional psilocybin on their own between 3 and 6 months after the study treatments. Removing these patients from the analysis did not alter the long-term results.

A total of 14 patients reported experiencing autobiographical visions, usually regarded as insightful and informative. The altered states of consciousness evaluation identified several items that differed between the low and high doses: experience of unity, spiritual experience,

blissful state, insightfulness, and complex imagery. When these interrelated items were combined into a single factor, the factor was significantly associated with improvement on the QIDS-SR.

Psilocybin was generally well tolerated. One patient had an "overwhelming," although "blissful" experience during high-dose psilocybin and refused some follow-up measures. Adverse effects of psilocybin included transient anxiety, headache, nausea, and paranoia. There were no flashbacks or persisting perceptual changes.

Carhart-Harris R, Bolstridge M, Day C, Rucker J, et al: Psilocybin with psychological support for treatment-resistant depression: six month follow-up. *Psychopharmacology* 2008;235 (February):399–408. From Imperial College London, U.K.; and other institutions. **Funded by the UK Medical Research Council; and the Alex Mosley Charitable Trust. The authors declared no competing interests.**

***See Reference Guide.**

Psychotic Symptoms in Parkinson's Disease

Although they consist of hallucinations and delusions, psychotic symptoms in Parkinson's disease differ greatly from positive symptoms of schizophrenia. Hallucinations are generally emotionally neutral, often consisting of people silently conducting activities in the margins of the patient's visual field. When acknowledged by the patient, the figures typically disappear. They return regularly, and can become a problem when the patient feels threatened by their appearance. In many cases, patients and their families are willing to tolerate benign hallucinations as medication-induced. Delusions in Parkinson's disease are generally paranoid and may precipitate agitation. Treatment may be required if the symptoms are bothersome and should be considered in anticipation of an increase in antiparkinsonian medications.

Before initiating treatment for psychosis in patients with Parkinson's disease, medical illnesses should be ruled out; infections can exacerbate Parkinson's disease and cause delirium with psychotic features. Next, possible medication associations should be evaluated as a contributing factor. Psychoactive drugs such as anxiolytics and antidepressants, anticholinergic medications for urinary incontinence, and pain medications may all contribute to psychotic symptoms. These drugs should be reduced to their lowest tolerated doses, and then medications for Parkinson's disease motor function should be assessed. The sequence for reducing these dosages should be individualized. It has been suggested that the dosage of anticholinergics, amantadine, dopamine agonists, and MAO-B inhibitors be reduced, in that order, before considering a reduction of L-dopa and COMT inhibitors. Worsening of parkinsonism should be anticipated when these drugs are reduced.

If the symptoms continue to require treatment, there are 2 medications with convincing evidence of efficacy in Parkinson's disease psychosis: pimavanserin (the only FDA-approved drug for the indication) and clozapine. Although not supported by clinical trial evidence, many clinicians have also reported good results with quetiapine. Pimavanserin is well tolerated and moderately effective. Clozapine appears to be highly effective in Parkinson's disease psychosis in the dosage range of 6.25–50 mg/day and does not compromise motor function. However, sedation, which can worsen delirium, along with neutropenia and agranulocytosis, are potential concerns.

Onset of pimavanserin efficacy may take 4–6 weeks, while clozapine may reduce symptoms within 1 week, suggesting that for patients who can tolerate symptoms temporarily, pimavanserin may be the best option while clozapine may be more beneficial when a rapid symptom reduction is required.

Friedman J: Pharmacological interventions for psychosis in Parkinson's disease patients. *Expert Opinion on Pharmacotherapy* 2018; doi 10.1080/14656566.2018.1445721. From Butler Hospital and Brown University, Providence, RI. **Funded by the NIH; and other sources. The author disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: amantadine—*Symmetrel*; clozapine—*Clozaril*; pimavanserin—*Nuplazid*; quetiapine—*Seroquel

Timing of Antidepressant Response

According to results of a meta-analysis of long-term acute treatment trials, patients whose depressive symptoms do not initially respond to antidepressant monotherapy may continue to experience improvements over 3 months without a change in their treatment. However, the likelihood of improvement after the first 12 weeks of nonresponse is relatively small.

Background: Current recommendations on how long to persist with acute antidepressant treatment vary widely, largely because of a scarcity of data on response and remission after 4–6 weeks. The present study was undertaken to estimate the time point at which the likelihood of response and/or remission ceases to increase.

Methods: The meta-analysis synthesized data from trials of clinically common treatment durations. The included studies compared antidepressant monotherapy with placebo in adults with unipolar major depressive disorder. Trials in patients with treatment-resistant disease and those in patients with concurrent disorders were included, but continuation trials were excluded because patients in these trials had already experienced response to acute medication. The eligible trials had continuous outcome reporting every 4 weeks for ≥12 weeks (and up to 24 weeks), during which time patients continued to receive their randomly assigned antidepressant or placebo. The primary outcome of the meta-analysis was the additional number of previously nonresponsive patients who met response criteria at each time point, with response defined as a ≥50% decrease in score on a standardized depression rating scale.

Results: A total of 9 studies, with 3466 patients, met the inclusion criteria. About two-thirds of the study patients received active medication (citalopram, desvenlafaxine, duloxetine, fluoxetine, levomilnacipran, mianserin, paroxetine, sertraline, or venlafaxine), and one-third received placebo.

Five studies had complete data through weeks 5–8 and 9–12. Previously nonresponsive patients continued to have response to medication during these periods, with about twice the likelihood as response to placebo. (See table.) Rates of remission also increased in previously unremitted patients receiving active medication, by 17% in weeks 5–8 and 13.5% in weeks 9–12. The corresponding remission rates in placebo-treated patients were 16% and 8%. Two studies had complete data on patients treated for 24 weeks. In these studies, response rates with both medication and placebo plateaued after week 12.

Rates of new response in patients previously nonresponsive to antidepressant or placebo

Weeks	Percentage of New Responders		Odds Ratio*	Number Needed to Treat*
	Drug	Placebo		
5–8	21.6%	13%	1.97	11
9–12	9.9%	2.4%	2.25	17

Discussion: These results suggest the additional likelihood of a response after 4 weeks may be substantial enough to weigh against the possible adverse effects of second-stage treatment strategies, at least until week 12. Previous evidence has suggested that if response is not achieved by week 12, switching to another antidepressant monotherapy may not be any more effective than continuing with the same drug. However, efficacy may be improved by

augmentation with lithium or a second-generation antipsychotic, adding a second antidepressant, increasing the dose of the initial antidepressant, or ECT.

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

Henssler J, Kurschus M, Franklin J, Bschor T, et al: 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. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11470. From the University of Cologne Medical School. Germany. **Funded by the University of Cologne; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; levomilnacipran—*Fetzima*; mianserin (not available in the U.S.)—*Tolvon*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor

***See Reference Guide.**

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

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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

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