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Biomarkers for Worsening Suicidal Ideation

In patients newly treated with an SSRI, worsening suicidal ideation was accurately predicted using a combination of clinical data and 2 molecular markers. The markers can be easily measured in peripheral tissues, making them potentially useful in clinical practice.

Methods: The aim of the study was to investigate the utility of 2 types of biomarker—messenger RNA (mRNA) and microRNA (miRNA)—to predict worsening of suicidal ideation during antidepressant treatment. Participants were 237 adults (mean age, 47 years; 70% women) experiencing a major depressive episode who were enrolled in a randomized, placebo-controlled, 8-week trial of duloxetine (*Cymbalta*). Suicidal ideation was assessed at baseline and throughout the trial using item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS), which ranks suicidal thoughts on a scale from 0 to 6. The primary study outcome, treatment-worsening suicidal ideation, was defined as an increase of ≥1 point on item 10 at any time during follow-up. Treatment-emergent suicidal ideation, a secondary outcome, was defined as an increase of ≥1 point on item 10 in patients with a baseline score of 0. RNA was assayed in blood samples using nearly 17,000 mRNA targets and 281 miRNA targets. Predictive value for treatment-worsening suicidal ideation was evaluated for 4 different models based on clinical data, mRNA, miRNA, and combining all 3 variables.

Results: During the study, suicidal ideation worsened in 32 study participants, 11 (9.8%) treated with duloxetine and 21 (16.8%) treated with placebo. Treatment-emergent suicidal ideation developed in 2 patients, both in the placebo group. The clinical predictive model analyzed a large number of variables related to patient demographics, history, and clinical presentation. Of these factors, only the baseline MADRS total score predicted worsening suicidal ideation, with an area under the curve (AUC)* of 0.66, a sensitivity* of 90.9%, and a specificity* of 42.6%. The mRNA and miRNA predictive models each identified 2 markers predictive of worsening suicidal ideation. Combining each type of marker (that is, both mRNAs and, separately, both miRNAs) resulted in models with comparable or somewhat better predictive performance than the MADRS. When all of the predictive factors were combined, the result was a model that incorporated the MADRS and 1 each of the mRNAs and miRNAs, resulting in an AUC of 0.94,

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sensitivity of 100%, and specificity of 89.1%. This model was significantly more accurate than the model based on the MADRS alone ($p<0.001$). When applied to the placebo group, the final model did not predict worsening suicidal ideation.

Discussion: Detailed clinical interviews are of limited accuracy in predicting worsening suicidal ideation during antidepressant treatment. Altered expression of mRNA has been identified in major depressive disorder and in relation to suicidal behavior. Although less well investigated, miRNAs have also been implicated in depression and suicide. The RNA markers identified in the present study have plausible links to processes that may factor in depression, including neurogenesis, neuronal plasticity, and fear and anxiety responses. However, the study results must be considered preliminary based on the relatively small sample size and the low frequency of worsening suicidal ideation. In addition, the study design did not allow for investigation of whether use of the predictive tool would be effective in other populations or if it could improve patient outcomes. Given the promising results and the relative ease of RNA assay, additional research appears to be warranted.

Belzeaux R, Fiori L, Lopez J, Boucekine M, et al: Predicting worsening suicidal ideation with clinical features and peripheral expression of messenger RNA and microRNA during antidepressant treatment. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12556. From McGill University, Montreal, Canada; and other institutions. **Funded by the Ontario Brain Institute; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Esketamine Nasal Spray in Resistant Depression

In a phase 3 clinical trial, esketamine nasal spray was superior to placebo when added to a newly initiated oral antidepressant in patients with treatment-resistant depression.[1] While the results are encouraging, concerns remain about the length of treatment, rapid relapse after discontinuation, and potential suicide risk, according to an editorial.[2]

Methods: The study enrolled patients with moderate to severe depression, resistant to ≥1 prior oral antidepressant in the current episode, plus a different antidepressant that was ongoing at the start of the study. After 4 weeks of observation on antidepressant treatment, patients who continued to meet study criteria for depression were started on a new antidepressant, chosen by their clinician from 4 commonly used SSRIs or SNRIs (i.e., escitalopram, sertraline, duloxetine, extended-release venlafaxine). At the same time, patients began using randomly assigned double-blind esketamine nasal spray, flexibly dosed twice per week at 56 or 84 mg, or placebo. The primary study endpoint was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) after 4 weeks of double-blind treatment. Patients were observed for withdrawal symptoms for 2 weeks after treatment discontinuation.

Results: Of 227 patients who began the randomized phase, 87% completed 4 weeks of treatment. Two-thirds of patients receiving esketamine were receiving the 84-mg dose by week 4. The mean MADRS score at baseline was 37 in both treatment groups. By study end, scores decreased by an average of 21 points in the esketamine group, compared with 17 points in the placebo group ($p=0.02$; effect size,* 0.3). Secondary efficacy endpoints were designed to be evaluated in a hierarchical scheme, but the first secondary endpoint, the proportion of patients with a ≥50% decrease in MADRS score by day 2 and persisting to the end of the study, did not differ statistically between the 2 groups (7.9% for esketamine, 4.6% for placebo). In post-hoc analyses, rates of response were 69% with esketamine and 52% for placebo (number needed to treat* [NNT], 6). Rates of remission (i.e., MADRS score ≤12) were 52.5% for esketamine and 31% for placebo (NNT, 5). No clear evidence of withdrawal was observed after esketamine discontinuation; nor were there reports of post-treatment drug abuse or cravings.

Discussion: The study failed to reach an anticipated between-treatment difference of 6.5 points on the MADRS. However, the observed 4-point difference exceeds minimal clinically important

differences reported in the literature. The criteria for clinical response (by day 2 and persisting throughout treatment) may have been overly strict. Response and remission in the placebo group occurred more frequently than anticipated.

Editorial. The phase 3 development program for esketamine included 3 pivotal trials, of which only the present one showed a statistically significant difference from placebo on the primary endpoint, and the effect size was in the modest range. While the difference from placebo appeared early and was maintained throughout treatment, it did not increase. This finding raises the question of whether esketamine needs to be continued beyond 1 or 2 weeks. Animal studies suggest prolonged treatment is necessary to maintain biological effects, but the optimal dosage and duration remain unknown. Finally, there have been 3 reports of suicide occurring 4–20 days after discontinuing esketamine, including 2 in patients with no prior evidence of suicidality, which may suggest a protracted withdrawal reaction.[3]

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

[1]Popova V, Daly E, Trivedi M, Cooper K, et al: Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *American Journal of Psychiatry* 2019;176 (June):428–438. doi 10.1176/appi.ajp.2019.19020172. From Janssen Research and Development, Beerse, Belgium; and other institutions. **Funded by Janssen Research and Development, Titusville, NJ. All study authors disclosed relevant financial relationships with commercial sources including Janssen.**

[2]Schatzberg A: A word to the wise about intranasal esketamine [editorial]. *American Journal of Psychiatry* 2019;176 (June):422–424. doi 10.1176/appi.ajp.2019.19040423. From Stanford University School of Medicine, CA. **The author disclosed potentially relevant financial relationships with commercial sources including Janssen.**

[3]US Food and Drug Administration: Briefing information for the Feb 12, 2019 joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). Available at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM630970.pdf.

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro*; esketamine nasal spray—*Spravato* sertraline—*Zoloft*; venlafaxine extended-release—*Effexor XR

***See Reference Guide.**

Adjunctive Esketamine for Depression Relapse Prevention

In a placebo-controlled withdrawal trial, adjunctive esketamine nasal spray (*Spravato*) reduced relapse risk by about 50% in patients with treatment-resistant depression.

Methods: Subjects could be enrolled in the study directly or transferred from 1 of 2 previously conducted trials. Direct-entry patients received esketamine nasal spray (56 or 84 mg, twice weekly) plus a new antidepressant for 12 weeks. Transferred patients had already achieved response (i.e., ≥50% decrease in the Montgomery-Asberg Depression Rating Scale [MADRS] score) to acute treatment with an antidepressant plus esketamine and received 12 weeks of esketamine optimized to maintain response at the lowest possible dosage, generally weekly or every other week. All patients had recurrent or prolonged single-episode depression of at least moderate severity that was resistant to ≥1 but ≤5 antidepressants. Remission was defined as a MADRS score of ≤12 for at least 3 of the 4 final weeks of the dose optimization phase. At the end of this phase, patients who had achieved stable remission or response were randomly assigned to continue active esketamine nasal spray or to placebo together with their prescribed antidepressant. Relapse was defined as a stable MADRS score of ≥22 or hospitalization for worsening depression or suicide event. Time to relapse following remission was the primary study outcome. However relapse following response (but not remission) was also evaluated.

Results: A total of 297 patients (mean age, 46 years; 197 women) were randomized to esketamine or placebo maintenance. Median exposure to esketamine was about 18 weeks, compared with 10 weeks for placebo. Esketamine maintenance was associated with a 51% lower risk of relapse

in patients who had achieved remission. (See table.) In addition, relapse risk was nearly 70% lower in patients who began with a stable response that was short of remission. About half of the relapses in the placebo group occurred during the first month after treatment with esketamine was discontinued. The study raised no new concerns about the safety or tolerability of esketamine.

Relapse During Maintenance with Esketamine or Placebo					
Patient status at start of maintenance	Number (%) of Relapses		Hazard Ratio*	Significance	Number Needed to Treat*
	Esketamine	Placebo			
Remission (n=176)	24 (27%)	39 (45%)	0.49	p=0.003	6
Response (n=121)	16 (26%)	34 (58%)	0.30	p<0.001	4

Discussion: A concern about randomized discontinuation trials is that patients who relapse could be experiencing antidepressant withdrawal. That is not likely to be the case with esketamine because its short half-life precludes steady-state levels with intermittent dosing. The high rate of early relapse is consistent with that following ECT. It is likely that relapses represent the greater vulnerability of patients with treatment-resistant depression during maintenance with antidepressant monotherapy.

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

Daly E, Trivedi M, Janik A, Li H, et al: Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1189. From Janssen Research and Development, LLC, Titusville, NJ; and other institutions. **Funded by Janssen. All study authors disclosed relevant financial relationships with commercial sources including Janssen.**

***See Reference Guide.**

Maintenance Treatment After Manic Episode

An observational study found that following hospitalization for a manic episode, patients receiving monotherapy are more likely to experience treatment failure than those receiving combination therapies. Despite the presumed lower tolerability of combination therapies, they were associated with lower rates of discontinuation and medication switch than monotherapy, while rehospitalization rates were generally not influenced by medication choice.

Background: Most observational studies have found lithium monotherapy superior to other drugs or combinations. However, these studies have failed to differentiate between discharges following mania or depression. The present study may be the first to compare the effectiveness of a wide range of drugs and multiple combinations following mania.

Methods: Study subjects were adults discharged from inpatient care after a manic episode between 2006 and 2014. The study compared outcomes with all medications approved to treat mania in Sweden (i.e., lithium, valproate, olanzapine, quetiapine, and aripiprazole), and their combinations. The primary study outcome, treatment failure, was a composite of medication discontinuation or switch and readmission to inpatient care, occurring within 1 year after discharge. Multiple readmissions for mania in a single individual were included. The analysis was adjusted for potential confounders including sociodemographic factors, factors related to the index hospitalization, and patient's psychiatric history.

Results: The analysis included data for >5700 hospitalizations in nearly 3800 patients; >1000 of the patients were hospitalized on ≥2 occasions during the study period. Slightly more than half

of patients (57.5%) were treated with monotherapy. A total of 4871 treatment failures (85%) occurred within 1 year of discharge—2677 medication switches, 1108 discontinuations of all treatment, and 1096 rehospitalizations despite ongoing medication. Outcomes were poorer in patients with comorbid borderline personality disorder, ADHD, autism spectrum disorder, and recent antidepressant use. Depot antipsychotics and a longer index hospitalization were associated with better outcomes.

In patients receiving monotherapy, rates of treatment failure ranged from 87% to 93% and were significantly higher for all atypical antipsychotics than for lithium. (See table.) The difference between valproate and lithium monotherapies was negligible. Among monotherapies, the risk of medication switch was higher for atypicals, while medication discontinuation was more common in patients taking valproate or olanzapine.

All Cause Treatment Failure Vs Lithium Monotherapy			
Drug Therapy	**# of Treated Patients**	**Failure Rate**	**Adjusted Hazard Ratio***
Lithium	n=1133	87%	Reference
Valproate	n=525	87.4%	1.01
Olanzapine	n=1013	93.3%	1.51
Quetiapine	n=468	90.2%	1.2
Aripiprazole	n=146	92.5%	1.28
Lithium + Valproate	n=217	83.4%	0.72
Lithium + Olanzapine	n=696	76.5%	0.69
Lithium + Quetiapine	n=314	79.6%	0.66
Lithium + Aripiprazole	n=92	79.3%	0.66
Valproate + Olanzapine	n=415	83.6%	0.82
Valproate + Quetiapine	n=171	76.6%	0.61
Valproate + Aripiprazole	n=50	86%	0.93
Olanzapine + Quetiapine	n=62	91.9%	1.2
Lithium + Valproate + Olanzapine	n=136	76.5%	0.55
Lithium + Valproate + Quetiapine	n=68	64.7%	0.4
Other Combinations	n=207	75.8%	0.62

Rates of treatment failure in patients receiving combination therapies were significantly lower than lithium monotherapy for all combinations except olanzapine+quetiapine. (See table.) The combination of lithium+valproate+quetiapine had the lowest overall risk of treatment failure, and was the only treatment associated with significantly lower rates of rehospitalization than lithium monotherapy.

Discussion: The authors acknowledge that the use of treatment failure as an outcome does not allow for collection of information on the specific relapse symptoms that most affect patients' lives—recurrence of manic symptoms, functioning, and quality of life. Nevertheless, treatment failure is a reasonable proxy for capturing both the efficacy and tolerability, and hence the real world effectiveness, of treatments.

Wingard L, Brandt L, Bodén R, Kieler H, et al: Monotherapy vs. combination therapy for post mania maintenance treatment: a population based cohort study. *European Neuropsychopharmacology* 2019; doi 10.1016/j.euroneuro.2019.04.003. From the Karolinska Institute, Stockholm, Sweden; and other institutions. **Funded by the Bror Gadelius Memorial Fund; and other sources. All study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; valproate—*Depakene, Depakote

***See Reference Guide.**

Benzodiazepines and Spontaneous Abortion

According to the results of a case-control study, benzodiazepine use in early pregnancy is associated with increased risk of spontaneous abortion.

Background: Benzodiazepines readily cross the placenta and have been identified at high concentrations in fetal tissues. They may play a role in steroidogenesis and cell proliferation and can interfere with fetal neurologic and immune system development, among other effects. Associations with spontaneous abortion have been previously reported, but earlier studies only investigated their effects as a class, despite known differences in their safety profiles.

Methods: The investigators analyzed data from the Quebec Pregnancy Cohort, a province-wide population-based study covering >400,000 pregnancies between 1998 and 2015. A case of spontaneous abortion was defined as any pregnancy loss between the 6th and 20th week of gestation. Each of these cases was matched for gestational age and calendar year with up to 5 control pregnancies. Incident benzodiazepine exposure, ascertained from a public prescription drug insurance database, was defined as a filled prescription between the last menstrual period and the index date (the date of the spontaneous abortion). Individual benzodiazepines evaluated included 6 short-acting agents with a half-life of ≤24 hours (i.e., alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam) and 5 longer acting agents (chlordiazepoxide, clonazepam, diazepam, flurazepam, nitrazepam). Dose-response effects were analyzed using diazepam equivalents. The analysis was adjusted for potential confounders known to influence benzodiazepine prescription or risk for spontaneous abortion, including maternal mood and anxiety disorders, insomnia, and use of antidepressant and antipsychotic medications.

Results: Spontaneous abortions occurred in 27,149 pregnancies (7%). A total of 1163 women were exposed to benzodiazepines during their pregnancy, 897 of whom (77%) filled only 1 prescription. The most frequently prescribed agents were lorazepam (45%) and clonazepam (23%). Rates of benzodiazepine use were 1.4% in women who had a spontaneous abortion, compared with 0.6% in those who did not. Risk estimates were statistically significant for benzodiazepines as a class, and were increased with each individual benzodiazepine, although not all increases were statistically significant. (See table.) The association between benzodiazepines and spontaneous abortion was dose-related, increasing from an odds ratio* of 1.73 with the lowest of 3 dose categories to 2.55 with the highest (p<0.01).

Benzodiazepine Exposures During Early Pregnancy and Risk of Spontaneous Abortion

Benzodiazepine Exposure	Women with Spontaneous Abortion (n=27,149)	Controls (n=134.305)	Adjusted Odds Ratio	Significance
All benzodiazepines	375 (1.4%)	788 (0.6%)	1.85	p<0.001
Short-acting benzodiazepines	284 (1.1%)	624 (0.5%)	1.81	p<0.001
Long-acting benzodiazepines	98 (0.4%)	178 (0.1%)	1.73	p<0.001
Alprazolam	33 (0.1%)	67 (0.1%)	2.02	p=0.002
Clonazepam	82 (0.3%)	138 (0.1%)	1.77	p<0.001
Lorazepam	180 (0.7%)	408 (0.3%)	1.75	p<0.001
Oxazepam	48 (0.2%)	112 (0.1%)	1.48	p=0.04

†Only medications associated with >20 spontaneous abortions and statistically significant associations are listed.

Discussion: The overall risk estimates in this study are consistent with other research and extend prior findings by linking risk of pregnancy loss to individual benzodiazepines, daily dosage, and both short- and long-acting medication classes.

Sheehy O, Zhao J, Bérard A: Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.0963. From the Centre Hospitalier Universitaire Sainte-Justine, Montreal; and the University of Montreal, Canada. **Funded by the Canadian Institutes of Health Research; and other sources. One study author disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

Common Drug Trade Names*: alprazolam—*Xanax*; bromazepam (not available in the U.S.)—*Lectopam*; clonazepam—*Klonopin*; diazepam—*Valium*; lorazepam—*Ativan*; nitrazepam (not available in the U.S.)—*Alodorm*; oxazepam—*Serax*; temazepam—*Restoril*; triazolam—*Halcion

***See Reference Guide.**

Genomics-Based Prediction of Antidepressant Outcome

Results of a retrospective study suggest a combination of genomic markers and baseline depression severity can be used to predict patients' response to SSRI therapy.

Methods: The predictive model was developed using data from 398 Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS) participants and then validated using data from 467 STAR*D participants and 165 participants in the International SSRI Pharmacogenomics Consortium (ISPC). All study subjects were treated with citalopram or escitalopram. The analysis was based on all subjects who had genotype and complete clinical data available at baseline and after 4 and 8 weeks of treatment. The genomic analysis included 6 single-nucleotide polymorphisms (SNPs) previously associated with SSRI pharmacodynamics, based on genome-wide association studies. Treatment outcomes were established using the clinician-rated Quick Inventory of Depressive Symptomatology (QIDS) or the Hamilton Rating Scale for Depression (HAM-D) at 4 and 8 weeks. Response was defined as a ≥50% reduction in either score. Remission was defined as a QIDS score of ≤5 or a HAM-D score of ≤7.

Results: Eight-week outcomes were not associated with most clinical or demographic data or with CYP2C19 metabolizer status. The top predictors of outcome in both sexes were the baseline HAM-D and 2 SNPs, both of which are biomarkers for plasma kynurenine. An additional SNP, associated with plasma serotonin, was a significant predictor only in men. Predictive accuracy of the model ranged from 71% to 88% depending on sex, outcome (response vs remission) and the symptom measure (QIDS vs HAM-D). These results were then externally validated using data from the STAR*D and ISPC studies. Accuracy in those populations was similar.

Discussion: Previous researchers have suggested that an accuracy of >70% in predicting antidepressant outcomes is clinically meaningful. The biomarkers used in this study were chosen based on their important roles in serotonin or kynurenine biosynthesis or in inflammation, processes known to be involved in depression. It is likely that additional SNPs are also predictive of response. If these results are replicated and extended to other antidepressants, the identified biomarkers could serve as genetic factors that could predict likelihood of treatment success or failure.

Athreya A, Neavin D, Carillo-Roa T, Skime M, et al: Pharmacogenomics-driven prediction of antidepressant treatment outcomes: a machine learning approach with multi-trial replication. *Clinical Pharmacology and Therapeutics* 2019; doi 10.1002/cpt.1482. From the University of Illinois at Urbana-Champaign; and other institutions. **Funded by the Mayo Clinic; and other sources. Five of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro

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Area Under the Curve (AUC): A statistical measures of discrimination—i.e., the ability to correctly classify those with and without a disease. An AUC value of 1 represents perfect accuracy, while a value of 0.5 has accuracy that is no better than chance.

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 (NNT): 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.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

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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