

JOURNAL WATCH[®]

PSYCHIATRY

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Do Transference Interpretations Help? Do They Stick?

A basic tenet of psychodynamic psychotherapy is that interpretation of patients' transference reactions toward their clinicians has therapeutic value. However, there is little experimental evidence to support this belief. Now, researchers report on the first-ever follow-up study of the long-term effects of transference interpretations in brief psychodynamic psychotherapy.

Previously, 100 patients in Norway seeking psychotherapy for symptoms of depression, anxiety, personality problems, and/or interpersonal problems had been randomized to a year-long course of weekly psychodynamic psychotherapy sessions with or without transference interpretations (*JW Psychiatry* Dec 2006, p. 93, and *Am J Psychiatry* 2006; 163:1739). Psychiatrists or a psychologist provided psychotherapy, which was carefully monitored for treatment fidelity. All but five patients completed the treatments. At treatment termination, patients receiving either type of psychotherapy had improved significantly and equivalently during the course of treatment, and patients with less-mature object relations had particularly benefited from transference interpretation therapy.

In the current report, the researchers demonstrate that gains in psychological functioning were robustly sustained at follow-ups 1 and 3 years later. Again, patients with a lifelong pattern of poor object relations who received psychotherapy with transference interpretations were significantly more improved than those who received the comparison treatment.

COMMENT:

Because the study lacked "no treatment" or "waiting list" controls, we cannot

assess the extent to which both treatments work or determine whether patients similar to these participants might naturally improve on their own over 1 to 4 years. However, the clear, sustained, and comparatively greater improvements after transference-interpreting psychotherapy among patients with historically poor object relations strongly suggest that this technique may offer long-standing benefits for such patients.

— **Joel Yager, MD**

Hoglund P et al. Transference interpretations in dynamic psychotherapy: Do they really yield sustained effects? Am J Psychiatry 2008 Jun; 165:763.

Copy Number Variants and Schizophrenia

Approximately 12% of the human genome consists of relatively common copy number variations (CNVs) — i.e., insertions or duplications of DNA sequences (*JW Psychiatry* Feb 2007, p. 17, and *Nature* 2006; 444:444). Rare CNVs, however, might be associated with some diseases — e.g., autism (*JW*

Psychiatry Apr 2008, p. 32, *Am J Hum Genet* 2008; 82:477, and *N Engl J Med* 2008; 358:667). Two research groups have now investigated rare CNVs in schizophrenia patients.

Walsh et al. genotyped two study populations. In 150 adults with sporadic or familial schizophrenia, the researchers found a significantly greater risk for rare CNVs than in matched healthy controls. The researchers found an even higher risk for rare CNVs in a group of 83 youths with childhood-onset schizophrenia and no major chromosomal anomalies, compared with 154 of their parents. The frequency of common CNVs did not differ significantly between adult patients and controls. Compared with the rare CNVs found in controls, those in the schizophrenia patients more frequently disrupted gene structure, and these were significantly over-represented in neurodevelopmental, RNA, and glutamate pathways.

Xu et al. genotyped a sporadic-schizophrenia cohort (152 adults with sporadic schizophrenia and their unaffected parents) and a familial-schizophrenia cohort (48 parent-child trios

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where a close relative also had schizophrenia). Controls were 159 healthy volunteers from the community and their parents. Again, rare CNVs were significantly more frequent in the schizophrenia cohorts than in the control group and more frequent in the sporadic cohort than in the familial cohort. Some of the rare CNVs were found in unaffected parents in the control and sporadic-schizophrenia groups.

COMMENT:

Previously, researchers into the genetics of schizophrenia tested common disease-common allele theories in genome-wide and candidate gene association studies, such as those on neuregulin (*JW Psychiatry* Feb 2007, p. 16, and *Nat Neurosci* 2006; 9:1477). The current findings extend the heterogeneity of schizophrenia pathogenesis to include rare CNVs. These are highly associated with sporadic schizophrenia. As these genetic complexities unfold, opportunities for developing targeted preventions or interventions will abound.

— **Barbara Geller, MD**

Walsh T et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 2008 Apr 25; 320:539.

Xu B et al. Strong association of de novo copy number mutations with sporadic schizophrenia. Nat Genet 2008 Jul; 40:880.

Emerging Perspectives: Psychotropic Drugs During Pregnancy — New Data on Neonatal Outcomes

We still know little about the neonatal risks from maternal use of psychotropic drugs during pregnancy, which limits accurate weighing of risks and benefits for expectant mothers. Three big observational studies provide new data.

Using large medical, demographic, and public drug insurance registries in Quebec, researchers focused on women with psychiatric diagnoses (mostly, mood or anxiety disorders) and antidepressant use for at least 1 month in the year before pregnancy. Researchers compared first-trimester antidepressant exposure and duration in 2140 healthy infants and 189 infants with any major congenital malformation in the year after birth. Antidepressants commonly used were paroxetine (42%), sertraline (15%),

and venlafaxine (13%). The risk for congenital malformation (8%, vs. the usual population rate of 3%) was unrelated to first-trimester antidepressant use, its duration, or therapeutic class. Controlling for ethnicity and for drug, alcohol, and tobacco use, determined in 806 mothers, did not alter results.

Other researchers linked maternal and neonatal British Columbian health records to identify recipients of a serotonin reuptake inhibitor (commonly, paroxetine, 39%; fluoxetine, 25%; or sertraline, 23%) during pregnancy and compared effects of early exposure only (first and/or second trimesters; n=1575) and of continued exposure (from first or second trimester through delivery; n=1925). Late exposure was significantly associated with lower birth weight, gestational age, and birth weight for gestational age, and with risks for respiratory distress and cesarean section. Because the two groups differed in maternal illness severity, the investigators used propensity scores to create two groups (n=429 each) matched for duration of exposure and illness severity; no between-group differences were found. When illness severity was controlled for, longer duration of exposure significantly increased the risks for lower birth weight, gestational age, and weight for age, and for respiratory distress.

A third group used prospective data from the U.K. National Teratology Information Service to compare gestational age and birth weight after exposure to typical and atypical antipsychotics (45 and 25 infants, respectively) or to drugs without adverse neonatal effects (38 infants). Postdate or premature birth, maternal diabetes, and congenital malformations were exclusions. The typical-antipsychotic group had higher incidences of small size for gestational age and lower mean birth weight than the group exposed to drugs without adverse neonatal effects. The atypical-antipsychotic group had a higher incidence of large size for gestational age than both comparison groups and heavier mean birth weight than the typical-antipsychotic group, even after adjustment for maternal use of weight-altering medications. These differences were more pronounced in a subanalysis of infants exposed to olanzapine or clozapine.

COMMENT:

The first study suggests that elevated rates of malformations are more likely related to maternal illnesses (or, possibly, to these participants' low socioeconomic status) than to the drugs used to treat them. In addition to highlighting the importance of controlling for severity of maternal psychiatric illness, the second study echoes this neurodevelopmental theme, suggesting that neonatal effects of SRIs are more likely due to their developmental effects than to drug withdrawal at birth. Avoiding these medications during the last trimester might reduce these adverse neonatal outcomes. Use of cognitive-behavioral therapy for depression and anxiety should be considered as an alternative to antidepressants during pregnancy, although this might not be adequate treatment for some.

Findings from the last study are more ominous, as large size for gestational age increases risks for diabetes and obesity; the metabolic effects of atypical agents might transfer to infants exposed to these medications.

— **Peter Roy-Byrne, MD**

Ramos E et al. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *Br J Psychiatry* 2008 May; 192:344.

Oberlander TF et al. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: Population-based study. *Br J Psychiatry* 2008 May; 192:338.

Newham JJ et al. Birth weight of infants after maternal exposure to typical and atypical antipsychotics: Prospective comparison study. *Br J Psychiatry* 2008 May; 192:333.

Antipsychotic Prescribing Trends in U.K. Children

Researchers have reported a 600% increase over a 10-year period in prescriptions of antipsychotics to pediatric outpatients in the U.S. (*JW Psychiatry* Jul 2006, p. 53, and *Arch Gen Psychiatry* 2006; 63:679). These authors examined pediatric antipsychotic prescriptions in the U.K.; the national general-practice database includes more than 789,000 patients aged 19 or younger. The investigators examined antipsychotic prescriptions, drug types, and diagnoses for three age groups (0–6, 7–12, and 13–19 years) from 1992 through 2005.

Prevalence of these prescriptions increased significantly, from 0.29 to 0.77 prescriptions per 1000 patient-years. The 7–12 age group had the greatest increase, followed by the 13–19 age group. Atypical-antipsychotic use also increased significantly. In the two younger groups, more than 50% of patients with antipsychotic prescriptions had diagnoses in the category of “behavior, conduct, and personality disorders.” In the oldest group, more than 50% of such patients had diagnoses of affective disorders.

COMMENT:

The authors calculate that over the same period as in the U.S. study, pediatric antipsychotic prescriptions in the U.K. increased by 36%. Some, but not all, of the large disparity in the size of these increases may be due to methodological differences. The U.S. study measured office visits that included an antipsychotic prescription, whereas the U.K. study focused on prescriptions written.

Most younger children who received antipsychotic prescriptions had nonpsychosis diagnoses; because general practitioners care for most children in the U.K., these nonspecialists might have underdiagnosed more-serious psychiatric disorders and, therefore, not referred these children to a specialist for initiation of antipsychotic medication. Alternatively, physicians may have prescribed major psychotropics for conditions that could be managed without these drugs. Data in two countries now appear consistent with the hypothesis that children are sustaining severer psychiatric symptoms, as is also evident in the increased prevalence of autism (*JW Psychiatry* Feb 2003, p. 13, and *JAMA* 2003; 289:49). — **Barbara Geller, MD**

Rani F et al. Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. *Pediatrics* 2008 May; 121:1002.

Rapid Serious Adverse Events with Antipsychotics in Dementia

Antipsychotic medications are increasingly used to treat agitation in elderly patients with dementia, even though this use has been associated with increased risks for adverse events. These researchers used Ontario administrative health data to examine the risk for serious adverse events (SAEs) result-

ing in hospitalization or death within 30 days of initiating antipsychotic treatment in elderly patients with dementia.

Patients were separated into study groups of community-dwelling patients and nursing-home residents. Patients receiving atypical antipsychotics were matched with those receiving typical antipsychotics and with those receiving no antipsychotic (almost 7000 patients in each of six groups). Among community-dwelling patients, SAEs occurred in 16.0% of the typical-antipsychotic group, 13.9% of the atypical group, and 4.4% of the control group (odds ratios: typicals, 3.8; atypicals, 3.2). In the nursing-home group, SAEs occurred in 11.6%, 9.4%, and 5.6% of the respective groups (ORs: typicals, 2.4; atypicals, 1.9). All classes of events showed the same pattern, including worse effects with typicals than with atypicals.

COMMENT:

This excellent analysis demonstrates that antipsychotic medications increase risks for serious adverse events and that typicals appear to be somewhat more risky than atypicals. Starting in June 2008, U.S. packaging of both antipsychotic types must carry boxed warnings against their use in treating dementia-related psychosis (http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm), which is a much less frequent target than agitation in this population.

In this study, the number needed to harm (NNH) is relatively low (atypicals: community-dwelling patients, 8; nursing-home patients, 14), indicating a very unfavorable risk-benefit ratio (i.e., much less favorable than for other psychotropic drugs in other conditions). The risk appears greater in community-dwelling patients than in nursing-home patients. The frequency of events is particularly

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striking given that the time frame was restricted to the initial 30 days after treatment initiation. These rates are likely underestimates because only serious events were studied, the follow-up was relatively short, and some events may have been avoided by discontinuing medication when early warning signs occurred. These findings are consistent with the U.S. Food and Drug Administration black-box warning and suggest that antipsychotics be prescribed with great caution in this population and only after consideration of all other possible interventions (see *Am J Psychiatry* 2005 162:1996).

— **Peter Roy-Byrne, MD**

Rochon PA et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008 May 26; 168:1090.

I've Got Rhythm, Who Could Ask for Anything More (to Avoid Relapse)?

Light, as a natural zeitgeber, is well known to affect mood. Social cues (e.g., meals, meetings, or exercise) also may entrain circadian rhythm. Does lack of social rhythms or their disruption result in mood instability that precipitates the onset of affective episodes? These researchers examined social rhythm regularity and its effect on vulnerability to bipolar episodes.

Approximately 20,500 college students were screened in two phases (self-reported inventory and diagnostic interview) to obtain 57 students with cyclothymic or bipolar disorder not otherwise specified and 149 students with bipolar II disorder (individuals with bipolar I were not studied). Fewer than one third received treatment during follow-up. The control group consisted of 208 healthy, demographically matched students. All participants completed a social rhythm regularity questionnaire, designed to quantify daily social rhythm patterns. They underwent structured interviews every 4 months that assessed symptoms and occurrence of affective-disorder episodes (mean follow-up duration, 33 months).

Compared with controls, students with bipolar disorders performed significantly fewer regular activities, although the frequency of endorsed activities was the same between groups. In survival analyses, both regularity and diagnostic

group predicted the time to affective, hypomanic, or manic episode. Less regularity predicted shorter time to onset of affective episode.

COMMENT:

Cause and effect are difficult to tease apart: Does a more severe affective disorder result in fewer activities, or does the lack of a regular schedule result in relapse? Another confounder is the undertreatment of most of these study participants. It is worthwhile for clinicians to explore the regularity of our patients' meals and exercise, in addition to sleep, and educate them about social zeitgebers. — **Jonathan Silver, MD**

Shen GHC et al. Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. Bipolar Disord 2008 Jun; 10:520.

Lost in Translation: Simvastatin for Neurofibromatosis Type 1

Clinical manifestations of neurofibromatosis type 1 (NF1) include learning disabilities, especially visuospatial impairments; MRIs show hyperintensities in the brains of NF1 patients. Previously, researchers using a mouse model of NF1 found that cognitive deficits markedly improved when the mice were treated with statin drugs. Now, researchers have examined whether the findings in mice would translate to children (two of the researchers have applied for a related U.S. patent).

In a double-blind, 12-week study, 62 children (age range, 8–16) were randomized to receive simvastatin or placebo. Groups were matched except for age, which analyses controlled for. At baseline and at 12 weeks, children underwent a comprehensive battery of visuospatial and other cognitive tests. Investigators also measured cholesterol levels and hepatic functioning in all participants and performed diffusion tensor imaging on 50 participants.

One simvastatin recipient dropped out for reasons unrelated to medication, and three placebo recipients did not adhere to the medication regimen. Both active-treatment and placebo groups showed stable or improved neuropsychological scores by 12 weeks, without statistical between-group differences. On univariate analysis, the simvastatin group improved significantly in a visuo-

spatial task, and the gain was greater in children with lower baseline functioning. MRI findings did not differ between groups. Among simvastatin recipients, levels of total and low-density lipoprotein cholesterol decreased significantly from baseline (decreases of 21% and 39%), but high-density lipoprotein cholesterol and triglyceride levels did not change.

COMMENT:

In this study, simvastatin performed no better than placebo. Despite these negative findings, this study remains important because of its translational nature and because a positive finding might have had implications for learning impairments in other diseases.

— **Barbara Geller, MD**

Krab LC et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: A randomized controlled trial. JAMA 2008 Jul 16; 300:287.

Keep Your Eye on Fluoxetine: Effects on Neuronal Plasticity in the Visual System

Although antidepressant drugs have immediate effects on levels of serotonin, norepinephrine, or both, the current hypothesis is that antidepressant efficacy depends on the promotion of hippocampal neurogenesis and synaptogenesis and increase in brain-derived neurotrophic factor (BDNF). These investigators performed several experiments in adult rats (see also *JW Psychiatry* Aug 2007, p. 66, and *Nat Neurosci* 2007; 10:679) to examine the effect of fluoxetine on functional changes in visual neuronal circuitry; response was assessed with visual evoked potentials.

First, the researchers studied the shift in ocular dominance in visual cortical neurons after monocular deprivation (MD). After 1 week of MD, fluoxetine-treated rats, but not vehicle-treated rats, demonstrated a marked shift in ocular dominance in favor of the nondeprived eye — a plastic modification seen only in early brain development. Intracortical infusion of diazepam in fluoxetine-treated rats inhibited this effect. The researchers also examined the recovery of visual function in adult rats after prolonged MD. Control rats did not regain binocularity, but fluoxetine-treated rats demonstrated a complete rescue of visual

acuity. Fluoxetine's effect on neurotransmitters and BDNF were also examined; fluoxetine treatment was accompanied by lower levels of gamma-aminobutyric acid and higher BDNF expression.

COMMENT:

This study associates fluoxetine with functional changes in a neuronal system. As the authors suggest, it would be important to investigate whether fluoxetine affects neuronal plasticity in other brain systems, such as those responsible for mood. Also, fluoxetine might be used for the treatment of amblyopia. Because the findings also suggest possible detrimental effects of drugs that act on the benzodiazepine receptor, studies of depressed patients treated with and without benzodiazepines should be conducted. The current findings suggest that fluoxetine's therapeutic mechanism in depression is related to neuronal plasticity; potential uses may extend beyond depression. — **Jonathan Silver, MD**

Maya Vetencourt JF et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 2008 Apr 18; 320:385.

Do Your Patients Borrow, Lend, or Trade Medications?

Even though clinicians carefully attend to what and how they prescribe, patients often act counter to their clinicians' wishes, expectations, and even knowledge. These researchers investigated medication sharing in an ethnically and geographically diverse community-based sample. They conducted personal interviews with 700 individuals (age range, 12–44) recruited in public spaces, 43% of whom were determined to have low health literacy.

Only 66% of respondents reported that they had never loaned nor borrowed a prescription medication. Seven percent loaned a prescription medicine to someone else, 11% borrowed a medication, and 16% did both. Medications most commonly shared were allergy medications (25%), pain medications (22%), antibiotics (21%), and psychotropic medications, such as SSRIs, benzodiazepines, or stimulants (7%). Sharing was associated with higher health literacy and using English as one's primary language.

COMMENT:

This study may underreport the extent of medication sharing in the community,

because respondents may not have been fully candid about their possibly illicit medication sharing. Rates of medication sharing also may be higher among specific clinical populations, such as psychiatric patients.

People sometimes share medications to assist friends or relatives in urgent situations. However, with frequent medication sharing, those in need do not obtain appropriate care; medication users do not receive proper instructions; recipients perceive treatments as ineffective because they are being taken incorrectly or for the wrong indications; the risks grow for adverse effects, including drug–drug interactions; those who lend their medications are less likely to adhere to their treatments; and, of course, the potential for substance abuse increases. Clinicians are advised to routinely, and nonjudgmentally, inquire about medication sharing by their patients, and to offer guidance regarding the potential harms.

— **Joel Yager, MD**

Goldsworthy RC et al. Beyond abuse and exposure: Framing the impact of prescription-medication sharing. Am J Public Health 2008 Jun; 98:1115.

Those Cytokines Make Me Sick

Infections and immunizations often cause “sickness behavior,” including malaise and difficulty in concentrating, because the body responds to the invading agent by increasing cytokine levels. British investigators examined the effect of this process on psychomotor function in a randomized, crossover study. Sixteen healthy men received placebo or typhoid vaccine, which induces cytokines without affecting body temperature, and then underwent cytokine plasma tests and two cognitive tests. One week later, participants crossed over to the other treatment arm.

Vaccination resulted in significant increases from baseline in plasma interleukin (IL)-6 (but not of IL-1 receptor antagonist or tumor necrosis factor α). On a task involving the visual cortices, functional MRI showed similar overall blood flow in these areas after placebo and vaccine administration; however, in the substantia nigra, blood flow was attenuated after vaccination.

On a task involving the ability to overcome distraction, response times and

numbers of errors were similar after placebo and after vaccine. However, after vaccination, greater increases in IL-6 were associated with significantly slower reaction times, suggesting a general slowing of motor responses to visual stimuli. Substantia nigra blood flow during this task also decreased after vaccination.

COMMENT:

Previous studies have associated psychomotor dysfunction with elevated cytokine levels. The current findings suggest that inflammation interferes with activity of the substantia nigra, a primary dopaminergic region that mediates the generation and coordination of mental and physical action. This helps to explain why sickness behaviors occur in illnesses as diverse as influenza and depression (see *JW Psychiatry* Jul 2008, p. 53, and *Arch Gen Psychiatry* 2008; 65:395). The authors conceptualize sickness behaviors as promoting adaptive reorganization of physiologic and psychological resources in response to a challenge. This concept is a new version of the half-century-old hypothesis of “conservation-withdrawal” (a physiologic state of reduction of energy expenditure and parasympathetic dominance when a challenge cannot be overcome immediately), which can also be seen as promoting the psychological state of adaptive regression in the service of the ego. Modern neurobiology confirms clinical observations of sickness behavior and explains why we want to go to bed when we feel sick and should avoid tasks requiring rapid psychomotor and, probably, cognitive responses.

— **Steven Dubovsky, MD**

Brydon L et al. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 2008 Jun 1; 63:1022.

Depression and Diabetes: Each Increases Risk for the Other

Cross-sectional associations between depressive symptoms and diabetes have been inconsistently confirmed by prospective studies capable of identifying causality. Using data from a prospective study of subclinical cardiovascular disease, researchers performed

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These summaries are reprinted from other publications in the Journal Watch series of medical literature surveillance newsletters.
— Peter Roy-Byrne, MD

St. John's Wort: Not Effective for Treatment of ADHD

St. John's wort (*Hypericum perforatum*) is a commonly used herb that inhibits reuptake of serotonin, norepinephrine, and dopamine. In a randomized, double-blind, controlled trial, a team of naturopathic and allopathic physicians compared symptom control in a cohort of 54 children with ADHD (mean age, 9.8 years) who received St. John's wort (300 mg, 3 times daily) or placebo for 8 weeks.

Treatment with St. John's wort as the sole therapy for ADHD failed to demonstrate benefit over placebo, based on blinded clinical evaluation and standardized assessments on the Clinical Global Impression Improvement Scale or the ADHD Rating Scale-IV at 1, 2, 4, 6, and 8 weeks. Adverse affects were similar in children who received placebo and St. John's wort. Quality-of-life scores also did not differ between groups.

COMMENT:

Few rigorous clinical trials of complementary therapies in children have been published. Despite the limitations of a small cohort and a short therapeutic trial, this carefully conducted study shows no benefit of St. John's wort as a single therapy for ADHD. This type of solid evidence is needed to help frustrated families weigh the benefits of alternative therapies when standard, approved treatments are unsatisfactory.
— **F. Bruder Stapleton, MD**

Weber W et al. *Hypericum perforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents.* *JAMA* 2008 Jun 11; 299:2633.

Info on Suicide: What's Available on the Net?

The Internet often is implicated as a possible cause or information source after highly publicized suicide-massacre tragedies. Previous studies have shown how suicide Web forums and suicide pacts have helped de-

pressed individuals facilitate their own suicides. Investigators report the results of an Internet search that they conducted in May 2007 to see what information about suicide was available.

The authors entered 12 broad terms based on the word "suicide" into the four most popular search engines (Google, Yahoo, MSN, and Ask). They compiled the 10 top-ranking sites for each term and search engine, yielding a total of 480 Web pages (hits), including 90 dedicated suicide sites: 45 encouraged, promoted, or facilitated suicide (prosuicide sites); 43 discussed the pros and cons of different methods without encouraging the act (factual sites); 62 offered support or promoted suicide prevention; and 59 discouraged suicide. Twelve chat rooms involved discussions about suicide methods. The most common top-ranking sites across searches were prevention and anti-suicide sites, prosuicide sites, and factual sites. However, about half of all listings, including nearly all factual information sites (e.g., Wikipedia), provided details about methods of suicide, such as speed, certainty of death, and likely amount of pain.

COMMENT:

Although antisuicide and prevention sites were among the most likely top-ranking listings, prosuicide sites were equally available. Factual sites might influence individuals by indirectly providing information about suicide methods. In addition to finding ways to limit access to prosuicide sites, increased accessibility to antisuicide and prevention sites during routine Internet searches is needed. Pediatricians need to counsel families of depressed teens about what is available on the Internet and how to openly discuss with their child the information that they might be viewing.
— **Robin Drucker, MD**

Biddle L et al. *Suicide and the internet.* *BMJ* 2008 Apr 12; 336:800.

Peer Supporters Might Prevent Onset of Smoking in Eighth-Graders

Many schools have programs to discourage students from smoking, but evidence for their effectiveness is inconsistent. Investigators in the U.K. evaluated an innovative program in

which peer supporters were trained to use informal social networks (rather than formal classroom presentations) to discourage students from smoking.

The peer-support program was implemented in 30 schools chosen randomly from 59 preselected schools; the remaining schools continued usual smoking education programs. In intervention schools, the 15% of eighth-grade students who were most respected and admired (according to surveys of all students) learned about the benefits of not smoking and the development of communication skills during a 2-day training session. For the next 10 weeks, these students had informal discussions about smoking with their peers (e.g., during lunchtime or the commute to school).

Overall smoking rates, as assessed by student surveys, increased from 6% at baseline to 20% at 2 years. The odds ratios for smoking in the intervention schools compared with control schools (adjusted for baseline differences) immediately after the intervention and at 1 and 2 years later were 0.75, 0.77, and 0.85, respectively. These differences were of borderline significance, perhaps because the withdrawal of several schools left the study slightly underpowered.

COMMENT:

Schools should certainly continue efforts to prevent smoking, and the effectiveness of these programs should be rigorously assessed. This study demonstrates that prevention programs can work, but more effective approaches are needed.
— **Bruce Soloway, MD**

Campbell R et al. *An informal school-based peer-led intervention for smoking prevention in adolescence (ASSIST): A cluster randomised trial.* *Lancet* 2008 May 10; 371:1595.

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two separate analyses to examine risk for depression or diabetes in patients with the other condition at baseline. Investigators excluded participants with cardiovascular disease (a depression risk factor) and examined potential confounders. Over 3 years, they measured blood glucose levels three times and depressive symptoms twice.

In 5201 participants without diabetes at baseline, depressive symptoms (Center for Epidemiologic Studies Depression Scale [CES-D] scores >16 or new use of antidepressants) significantly but modestly increased risk for type 2 diabetes at 3 years (relative hazard [RH], 1.37). The risk was lower but still significant after adjustment for body-mass index, metabolic factors, socioeconomic status (SES), and inflammatory markers (RH, 1.10), but not after adjustment for lifestyle factors, although the RH was similar.

In 4847 participants without depressive symptoms at baseline, treated type 2 diabetes was significantly associated with depression at 3 years. This risk remained elevated after adjustment for BMI, SES, lifestyle, and diabetes severity (odds ratio, 1.52) and after exclusion of subjects using antidepressants (possibly for diabetic neuropathy). In contrast, impaired fasting glucose was associated with lower depression risk (OR, 0.79); after adjustment for confounders, the OR was similar but no longer significant.

COMMENT:

This study's examination of both hypotheses in one cohort and assessment of potential confounders are major strengths. The CES-D is not a diagnostic instrument, but its cutoff scores have been validated against diagnosis and identify depressive symptoms of potential clinical severity.

Neuroendocrine markers of depression might explain how depression leads to diabetes but were not examined. Treated diabetes could lead to depression via the stress of medical complications and diabetes management, two factors not present in patients with impaired glucose tolerance. The finding that impaired glucose tolerance reduces depression risk may relate to unmeasured confounders and needs replication.

— *Peter Roy-Byrne, MD*

Golden SH et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008 Jun 18; 299:2751.

Management of Depression in Cancer Patients

Little evidence guides depression treatment for cancer patients. To examine the effectiveness and cost-effectiveness of supplemental care provided by nurse care managers, researchers in the U.K. focused on a heterogeneous group of depressed cancer patients with a prognosis of at least 6 months.

After a two-stage screening and diagnostic interview, 200 patients meeting DSM criteria for major depression were randomized to usual care plus the intervention or to usual care only; another 134 patients refused to participate. The nurses delivered 3 months of psychoeducation (including promoting adherence to antidepressant regimens) and problem-solving therapy (to improve coping skills) and communicated with primary care physicians and oncologists; another 3 months consisted of telephone follow-up. Patients doing poorly could receive booster sessions. Intervention patients averaged seven sessions (only 3 attended no sessions), mostly at the cancer center. Telephone diagnostic interviews supplemented self-ratings.

Overall, 11% of patients saw mental health specialists. Depressive symptoms improved more in intervention patients than in controls at 3 months (effect size, 0.43); improvement persisted at 12 months. Significantly more intervention patients took therapeutic doses of antidepressants (supplied by primary care physicians) at 3 months (69% vs. 42% of controls) and 6 months (65% vs. 34%). Intervention patients showed greater rates of response (53% vs. 34%) and remission (29% vs. 14%) at 3 months and greater improvements in fatigue and anxiety. The intervention cost US\$670 over 6 months, with a cost per quality-adjusted life-year (QALY) of US\$10,556.

COMMENT:

A simple delivery mechanism can improve depression outcomes in cancer patients, with a cost per QALY that compares favorably to that of many cancer treatments (often, \$20,000 per QALY).

Diagnostic interviews verified self-ratings and eliminated self-report bias. Limitations were the exclusion of poor-prognosis patients and the refusal to participate by 40% of eligible patients (although this is typical of the standard clinical trial). Because depression is often overlooked in cancer patients or is attributed to the stress of having cancer, this study has high public health importance.

— *Peter Roy-Byrne, MD*

Strong V et al. Management of depression for people with cancer (SMaRT oncology 1): A randomised trial. Lancet 2008 Jul 5; 372:40.

Risk Factors for Postictal Psychosis: It's Not the Temporal Lobe

Postictal psychosis (PIP) occurs within 1 week after a seizure or seizure cluster in approximately 6% of individuals in video EEG (VEEG) monitoring studies. The common clinical wisdom dictates that this phenomenon is more common in temporal lobe epilepsy. In a case-control study, researchers retrospectively examined the risk factors for PIP among 153 consecutive patients with partial epilepsy who were undergoing VEEG for presurgical evaluation; 59 of the patients had experienced PIP, and 94 (controls) had not.

All participants had a clinical psychiatric interview. Psychosis was defined according to the DSM-IV: hallucinations, delusions, or grossly disorganized behavior. Patients who had other psychiatric or medical conditions that could explain the presence of psychosis (e.g., use of steroids or schizophrenia) were excluded.

Predictors of PIP included a history of encephalitis, family history of seizures or psychiatric disorders, interictal bilateral epileptiform activity, extratemporal or indeterminate localization of seizures, and secondarily generalized seizures.

COMMENT:

Clinicians' greater experience with PIP in temporal lobe partial epilepsy (because this is a common type of epilepsy) probably accounts for previous impressions of the temporal lobe predilection for PIP. When carefully examined, it is, in fact, extratemporal partial epilepsy that is associated with increased

Can you answer the following question about the summary "Copy Number Variants and Schizophrenia" (on page 61)?

Two research groups investigated possible links between schizophrenia and rare copy number variations (CNVs). Which statement is *not* correct?

- A. Adults with schizophrenia and youths with childhood-onset schizophrenia had significantly greater risks for rare CNVs than did those in comparison groups.
- B. Rare CNVs found in schizophrenia patients more frequently disrupted gene structure than those found in controls.
- C. Rare CNVs were more frequent in the familial-schizophrenia cohort than in the sporadic-schizophrenia cohort.
- D. The study findings support the theory that schizophrenia pathogenesis is heterogeneous, by adding rare CNVs as possible causes.

* Category: Psychiatry
Exam Title: JW Psychiatry: Schizophrenia
Posted Date: Jul 2 2008

CME Faculty: Michael Miller, MD

This is one of four questions in a recent Journal Watch Online CME exam. Click on the CME link from the Journal Watch summary online at*

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risk for PIP. Other genetic and etiologic factors further increase this risk.

—**Jonathan Silver, MD**

Alper K et al. Postictal psychosis in partial epilepsy: A case-control study. Ann Neurol 2008 May; 63:602.

Don't Talk and Drive?

In this era of multitasking, people commonly talk while driving. Many jurisdictions prohibit the use of hand-held cell-phones, but hands-free calls might be no safer: Certain verbal tasks can disrupt executive processing. Thinking of what to say and speaking take greater cognitive resources than listening. Additional resources may be required when the conversation is with an unseen person or when the voice does not originate from in front of the subject. These researchers examined how several of these factors affect performance of vision-based tasks.

College students listened to recorded instructions for accomplishing tasks, such as constructing a compost pile, and were intermittently asked for verbal

responses to related questions. The voice could come from speakers in front of, behind, or to either side of the participant. Meanwhile, the students performed one of two vision-based computer tasks (47 participants each): a target detection task, with both easy and more difficult matches, and a target pursuit task.

Compared with listening, speaking or planning to respond worsened performance on both visual tasks. The greater the difficulty of the first task, the worse was the performance. On the second task, planning to speak had a more negative effect than speaking, except when participants heard the voice from in front, which slightly reduced interference.

COMMENT:

To extend these findings to driving, one might hypothesize that hands-free talking impairs visual-task performance unless the voice is coming from in front of the driver. Thus, earpieces might not be a satisfactory solution. However, does this impairment also occur when talking (or preparing to talk) to passengers,

who are necessarily next to or behind the driver? I would expect greater impairment in people older than these student subjects and in those with preexisting attentional problems. These interesting preliminary data are not yet sufficient to change policy (but until then, I'm asking my taxi drivers not to use the hands-free phone).

—**Jonathan Silver, MD**

Almor A. Why does language interfere with vision-based tasks? Exp Psychol 2008; 55:260.

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