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Pimavanserin and Antidepressant Response

In a manufacturer-sponsored, multicenter, phase 2 trial, pimavanserin (*Nuplazid*) enhanced the efficacy of antidepressant therapy in patients with inadequate treatment response. Pimavanserin was free of the safety and tolerability concerns of the atypical antipsychotics often used to treat resistant depression.

Background: The atypical antipsychotic pimavanserin, indicated for treatment of psychosis in Parkinson's disease, has a unique mechanism of action relative to other antipsychotics; it is a potent antagonist and inverse agonist at the 5-HT_{2A} receptor with weaker activity as a 5-HT_{2C} antagonist/inverse agonist. It has no adrenergic, dopaminergic, histaminergic, or muscarinic receptor activity. It's receptor binding profile is similar to other drugs that have antidepressant efficacy.

Methods: This multicenter study was conducted in patients with major depressive disorder, with the current episode lasting ≥1 year, a baseline Montgomery-Asberg Depression Rating Scale score of >20, and a Clinical Global Impression Severity rating of at least moderately ill. Patients had a history of inadequate response to 1 or 2 adequate SSRI or SNRI trials (≥8 weeks each) during the current episode. Initially patients were randomly assigned to receive 5 weeks of treatment with 34 mg/day pimavanserin or placebo, added to their current SSRI or SNRI. Nonresponse was defined as a <50% decrease in the 17-item Hamilton Rating Scale for Depression (HAM-D) or a total score of >14. During a second 5-week study phase, placebo responders continued to receive placebo, placebo nonresponders were re-randomized to pimavanserin or placebo, and patients initially assigned to pimavanserin continued the drug. Antidepressant therapy was continued unchanged. The primary study endpoint was change from baseline in HAM-D score.

Results: A total of 203 patients were included in the analysis, 152 initially assigned to placebo and 51 assigned to pimavanserin; 58 placebo nonresponders were re-randomized in the second study phase. At baseline, mean HAM-D scores were 23 and 22 in the pimavanserin and placebo groups, respectively. At the end of stage 1, scores were decreased to 11.5 in the pimavanserin group, compared with 14.5 in the placebo group (effect size,* 0.63; p=0.0003). Pimavanserin

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separated statistically from placebo as early as the first weekly follow-up (p=0.037). Response and remission rates were significantly higher in the pimavanserin group (p<0.05), with numbers needed to treat* of 3.6 and 8.1, respectively.

Following re-randomization in stage 2, the reduction in HAM-D score did not differ between the pimavanserin and placebo groups (additional decreases of about 3 points). Analysis of patients who received 10 weeks of continuous treatment with pimavanserin (n=52) or placebo (n=126) supported the significant advantage for pimavanserin. Final HAM-D scores in this group averaged about 9 and 14 points, respectively (effect size, 0.5; p=0.007). Improvements in Sheehan Disability Score, the primary secondary outcome measure, paralleled those on the HAM-D in all analyses.

Pimavanserin was well tolerated. The most common adverse effects were dry mouth, nausea, and headache; each affecting about 10% of treated patients. Rates were similar with placebo. Pimavanserin was not associated with metabolic dysregulation, sexual dysfunction, or extrapyramidal symptoms.

Discussion: Efficacy of pimavanserin appeared to be particularly robust during stage 1 when all randomized patients were included in the analysis. Although stage 2 results indicate no significant differences between the groups, this is likely due to the substantially smaller sample size and the fact that patients who responded to placebo in stage 1 were not included. The authors note that the effect size for pimavanserin in the first study phase (0.63) is larger than those generally reported for adjunctive atypical antipsychotics (0.27–0.43). Additionally, pimavanserin did not produce the weight gain and metabolic disturbances often associated with the atypicals.

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

Fava M, Dirks B, Freeman M, Papakostas G, et al: A phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and inadequate response to therapy (CLARITY). *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.19m12928. From Massachusetts General Hospital and Harvard Medical School, Boston, MA. **Funded by Acadia Pharmaceuticals Inc. All 9 study authors disclosed potentially relevant financial relationships, including 9 with Acadia.**

***See Reference Guide.**

Testosterone for HSDD in Women

According to a global consensus statement endorsed by multiple national womens' health agencies, evidence supports the use of oral testosterone therapy for hypoactive sexual desire disorder/dysfunction in postmenopausal women. Although the treatment is not associated with serious adverse effects, benefits appear to be modest. Data regarding testosterone treatment of premenopausal women is insufficient to make recommendations.

Associations between endogenous androgen levels and sexual function in women are unclear, and no blood level cutoff has been established to differentiate between women with and without sexual dysfunction. However, based on a systematic review and meta-analysis of randomized controlled trials, the panel concluded that testosterone therapy, in doses that approximate physiological testosterone concentrations in premenopausal women, has positive effects on sexual function in naturally or surgically postmenopausal women. The benefits include small increases in the average number of satisfying sexual events per month, as well as improvements in sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness. Importantly, treatment is also associated with a reduction in distress related to sexual dysfunction. Available data do not support positive effects of testosterone therapy on general wellbeing, depressive symptoms, or cognitive function.

Treatment may be associated with a mild increase in acne and body/facial hair growth in some women, but more serious adverse effects are not expected in most patients. However,

oral testosterone therapy may have negative effects on cholesterol levels, and deep vein thrombosis, which may be related to concurrent estrogen use. Because women with high cardiometabolic risk and those with a history of breast cancer were excluded from clinical trials, use in these populations should be undertaken cautiously.

Because HSDD has multiple etiologies that can include psychosocial factors such as interpersonal difficulties and psychological distress, treatment should follow a biopsychosocial model and include pharmacologic options (e.g., hormonal therapies and/or other pharmacologic agents), psychotherapy, or multimodal treatments that combine both treatments. If testosterone therapy is prescribed, oral formulations should be used. Injectables, pellets, and other formulations can produce supraphysiological blood concentrations and the panel does not recommend their use. Even with oral therapy, total testosterone concentration should be measured before and 3–6 weeks after starting treatment. Additionally, women should be monitored for signs of androgen excess and serum testosterone should be measured at 6-months intervals. If no benefit is experienced by 6 months, testosterone treatment should be discontinued.

Davis S, Baber R, Panay N, Bitzer J, et al: Global consensus position statement on the use of testosterone therapy for women. *Journal of Endocrinology and Metabolism* 2019; 104 (10):4660–4666. doi 10.1210/jc.2019-01603. From Monash University, Melbourne, Australia; and other institutions. **Funded by the International Menopause Society; and other sources. Eleven of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Oral Antipsychotics: Comparative Efficacy, Tolerability

A large meta-analysis found few clinically relevant differences in overall efficacy between available antipsychotics. However, differences exist for specific symptoms and adverse effect liability.

Methods: A comprehensive literature search identified all published and unpublished randomized controlled trials comparing antipsychotics with each other or placebo in adults experiencing acute symptoms of schizophrenia or a related disorder. Studies were excluded if patients were experiencing their first-episode, were considered treatment-resistant, or had predominantly negative or depressive symptoms or concomitant medical illnesses. All oral second-generation (atypical) antipsychotics available in the U.S. or Europe and commonly used first-generation (typical or conventional) antipsychotics were evaluated. The primary outcome was change in schizophrenia symptoms, measured using a validated rating scale. Secondary outcomes included adverse effects, all-cause discontinuation, as well as response and improvements in positive, negative, and depressive symptoms.

Results: A total of 402 studies including >53,000 participants who were randomly assigned to 32 different antipsychotics or placebo were included in the network meta-analysis.* The pooled population had a mean age of 37 years, 56% of participants were male, and the mean illness duration was 12 years.

All antipsychotics reduced overall symptoms to a greater degree than placebo, although the difference was not statistically significant for several older agents. Compared with placebo, standardized mean differences* (SMD) ranged from 0.03 to 0.89 for overall symptoms, from 0.17 to 0.69 for positive symptoms, from 0.10 to 0.62 for negative symptoms, and from 0.10 to 0.90 for depressive symptoms. (See table, next page.) Of the agents available in the U.S., clozapine showed the greatest efficacy for all symptom categories. Olanzapine and risperidone were also significantly more effective for the primary outcome than other antipsychotics. Overlapping confidence intervals suggest that differences between most individual drugs were not significant.

Risk ratios (RR)* for all-cause discontinuation ranged from 0.52 to 1.15, and risk was greatest with pimozide. Risk for individual adverse effects varied widely. Zotepine produced the largest weight gain, prolactin elevation was greatest with paliperidone, and Qtc effects were

most prominent with sertindole. Risk for sedation was greatest with zuclopenthixol, and pimozide was associated with the greatest need for antiparkinson medication.

Efficacy and Tolerability of Oral Antipsychotics vs Placebo±							
	Overall Efficacy (SMD)	**Positive Symptoms (SMD)**	**Negative Symptoms (SMD)**	**All Cause Discontinuation (RR)**	**Weight gain (SMD)**	**Prolactin increase (SMD)**	**Sedation (RR)**
Atypical / Second-generations							
Aripiprazole	0.41	0.38	0.33	0.80	0.48	-7.1	1.46
Asenapine	0.39	0.47	0.42	0.84	1.21	5.05	2.17
Brexpiprazole	0.26	0.17	0.25	0.89	0.70	0.95	1.64
Cariprazine	0.34	0.30	0.32	0.93	0.73	-3.19	1.12
Clozapine	0.89	0.64	0.62	0.76	1.89	-77.1	3.02
Iloperidone	0.33	0.30	0.22	0.79	2.18	4.79	1.36
Lurasidone	0.36	0.33	0.29	0.88	0.32	7.04	1.75
Olanzapine	0.56	0.53	0.45	0.69	2.78	4.47	2.17
Paliperidone	0.49	0.53	0.37	0.70	1.49	48.51	1.33
Quetiapine	0.42	0.40	0.31	0.85	1.94	-1.17	3.27
Risperidone	0.55	0.61	0.37	0.82	1.44	37.98	2.03
Ziprasidone	0.41	0.43	0.33	0.90	-0.16	2.75	2.91
Typical / First-generation							
Chlorpromazine	0.44	0.57	0.35	0.91	2.37	8.70	2.55
Fluphenazine	0.24	—	—	0.89	—	—	1.09
Haloperidol	0.47	0.49	0.29	0.90	0.54	18.49	1.92
Loxapine	0.45	—	—	0.78	1.09	—	2.20
Molindone	0.42	—	—	0.86	0.56	—	1.40
Penfluridol	0.39	—	—	0.97	—	—	1.24
Perazine	0.29	—	—	0.79	1.02	-13.44	2.96
Perphenazine	0.56	0.45	0.42	0.79	—	—	1.11
Pimozide	0.30	—	—	1.15	—	-3.91	0.92
Thioridazine	0.54	—	—	0.76	—	—	2.63
Thiotixene	0.63	—	—	0.71	—	—	2.72
Trifluoperazine	0.24	—	—	0.98	2.32	—	1.53

±Only drugs approved in the U.S. are listed; Negative SMD values favor the antipsychotic over placebo; — not evaluated

Discussion: Many drugs are available for the treatment of schizophrenia and there is considerable variability in their receptor affinity profiles, which could lead to differences in efficacy and safety. A clear understanding of the relative risks and benefits among the agents is necessary to make informed treatment decisions. These results suggest that both older and newer drugs reduce overall symptoms of schizophrenia with differences based on specific symptoms. As expected, older antipsychotics were generally associated with more extrapyramidal adverse effects and prolactin elevation. Newer agents generally produced more weight gain and sedation.

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

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, et al: Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; 354 (September):939–951. doi 10.1016/S0140-6736(19)31135-3. From the Technical University of Munich, Germany; and other institutions. **Funded by the German Ministry of Education and Research; and the NIHR Oxford Health Biomedical Research Center. Three of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **aripiprazole—*Abilify*; asenapine—*Saphris*; brexpiprazole—*Rexulti*; cariprazine—*Vraylar*; chlorpromazine—*Thorazine*; clozapine—*Clozaril*; fluphenazine—*Prolixin*; haloperidol—*Haldol*; iloperidone—*Fanapt*; loxapine—*Loxitane*; lurasidone—*Latuda*; molindone—*Moban*; olanzapine—*Zyprexa*; paliperidone—*Invega*; penfluridol—*Semap*; perazine—*Taxilan*; perphenazine—*Triavil*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; thioridazine—*Mellaril*; thiotixene—*Navane*; trifluoperazine—*Stelazine*; ziprasidone—*Geodon***

***See Reference Guide.**

Brexpiprazole: Weight and Metabolic Effects

Combined data from randomized clinical trials indicate that adjunctive brexpiprazole (*Rexulti*) is associated with small effects on lipids and glucose metabolism and moderate weight gain in patients with depression.

Methods: This analysis was based on data from the manufacturer's placebo-controlled trials of adjunctive brexpiprazole in patients with insufficient response to antidepressant medications. Included were 4 short-term studies of similar design and 1 long-term safety study. In the short-term studies, patients who still met criteria for inadequate response after an 8- to 10-week trial of a clinician-selected open-label antidepressant plus placebo (n=1903) were randomized to receive 6 weeks of fixed or flexible dose brexpiprazole in the range of 1–3 mg/day or to continue placebo. Afterward, regardless of their brexpiprazole exposure in the parent study, patients from 3 of the trials (n=2944) entered the long-term safety study. The planned duration of the safety study was 52 weeks, but the design was amended to 26 weeks after the safety profile of brexpiprazole was considered to be adequately established.

Results: Data on weight gain were included from all short-term studies. However, because metabolic parameters were not assessed in 1 of the studies, the metabolic analysis included data from only 3 studies. In the pooled analysis of short-term studies, by week 6 patients treated with brexpiprazole gained an average of 3.3 lbs, compared with <1 lb in the placebo group. After a further 26 weeks of treatment, mean weight gain was 6.4 lbs with brexpiprazole. The subset of patients followed for 52 weeks gained an average of 8.4 lbs in total. Nearly 25% of patients enrolled in the long-term study gained ≥7% of their initial weight.

Mean changes in glucose and lipid parameters were generally small and were more likely to be in a favorable direction. However, triglyceride levels increased by a mean of 15.83 mg/dL over 52 weeks. Shifts in metabolic parameters were not related to brexpiprazole dosage.

Discussion: Brexpiprazole has a relatively a low affinity for histamine H_1 receptors, which may reduce its potential to cause diabetes and weight gain relative to some other atypical antipsychotics In addition, it is less likely than other atypicals to produce activating or sedating adverse effects and has no clinically relevant effect on prolactin, electrocardiogram, vital signs, or

other laboratory parameters. The authors note that because of the studies designs, the relative contribution of background antidepressants to weight gain and metabolic changes is unclear.

Editor's Note: Four of the 5 studies included in this analysis were previously covered in *Psychiatry Drug Alerts*. See the September 2015, August 2018, and August 2019 issues for more information on study designs, enrollment, and outcomes.

Newcomer J, Eriksson H, Zhang P, Meehan S, et al: Changes in metabolic parameters and body weight in patients with major depressive disorder treated with adjunctive brexpiprazole: pooled analysis of Phase 3 clinical studies. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12680. From Thriving Mind South Florida, Miami; and other institutions including H. Lundbeck A/S, Valby, Denmark, and Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ. **Funded by Otsuka and H. Lundbeck. All study authors disclosed potentially relevant financial relationships with commercial sources including Otsuka or H. Lundbeck.**

Inhaled Loxapine for Acute Agitation

Loxapine is a first-generation antipsychotic recently formulated for intranasal administration via a hand-held device. The device delivers a single inhalation of drug, which begins systemic absorption in <1 second and reaches peak plasma levels in 2 minutes. The half-life is 8 hours. Structurally similar to clozapine, loxapine is a post-synaptic dopamine D_2 receptor and serotonin 5-HT_{2A} receptor antagonist. No other antipsychotic is available as an inhaled formulation.

In clinical trials of acute agitation, the number needed to treat* to achieve response (≥40% decrease in the Positive and Negative Syndrome Scale–Excited Component from baseline to 2 hours) with inhaled loxapine was ≤4. This compares favorably with oral antipsychotics used to treat agitation. Surveyed patients considered treatment with inhaled loxapine preferable to oral or intramuscular agents.

Because administering inhaled loxapine requires patient cooperation, it may not be appropriate for individuals with severe agitation. The product labeling includes a black-box warning about bronchospasm, and the agent must be administered as part of a Risk Evaluation and Mitigation Strategy (REMS) program. In the clinical trials, all airway adverse events were mild or moderate. Other common adverse effects were taste distortion and throat irritation.

Time to Maximum Concentration of Common Agents for Acute Agitation	
Oral	
Lorazepam	20–30 minutes
Haloperidol	2–6 hours
Risperidone	60 minutes
Olanzapine	5–8 hours
Asenapine	30–90 minutes
Intramuscular	
Lorazepam	20–30 minutes
Haloperidol	20–60 minutes
Ziprasidone	15–60 minutes
Olanzapine	15–45 minutes
Aripiprazole	1–3 hours
Intravenous	
Haloperidol	Immediate
Intranasal	
Loxapine	2 minutes

Faden J, Citrome L: Examining the safety, efficacy, and patient acceptability of inhaled loxapine for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. *Neuropsychiatric Disease and Treatment* 2019;15:2273–2283. doi 10.2147/NDT.S173567. From Temple University, Philadelphia, PA; and New York Medical College, Valhalla, N.Y. **Source of funding not stated. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; asenapine—*Saphris*; clozapine—*Clozaril*; haloperidol—*Haldol*; lorazepam—*Ativan*; loxapine—*Adasuve*; olanzapine—*Zyprexa*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Zolpidem and Suicide Risk in Depression

In a placebo-controlled trial, adding zolpidem to antidepressant medication improved insomnia in patients with major depressive disorder (MDD) but did not have the expected effect on the study's primary outcome measure of suicidal ideation.

Background: Insomnia is a recognized risk factor for suicidal ideation, but the effects of its pharmacological treatment have not been systematically investigated in patients with depression.

Any possible improvement must be weighed against the possibility of worsening depression, suicidal thoughts and actions (including completed suicides), which have been reported with the use of sedative/hypnotics.

Methods: Patients with MDD, confirmed by structured clinical interview, who also met American Academy of Sleep Medicine criteria for insomnia were recruited via advertising and self-referrals to psychiatry clinics. Study participants were required to have a Hamilton Rating Scale for Depression (HAM-D) score of ≥20 and a score of ≥3 on the self-rated Scale for Suicidal Ideation (SSI). Those with a lifetime history of bipolar disorder, schizophrenia, or substance abuse, or with suicidal plans or intent were excluded. Patients were also required to be free of psychotropic medications for ≥1 week before randomization. Eligible patients (n=103; mean age, 41 years; 62% women) began open-label treatment with 20 mg/day fluoxetine, 50 mg/day sertraline, or 20 mg/day citalopram. Fluoxetine was prescribed for all patients unless they strongly preferred sertraline (n=3) or citalopram (n=5). Dosages could be doubled after 4 weeks if the HAM-D score was >15. Participants were randomly assigned to 8 weeks of treatment with 6.25 or 12.5 mg/day zolpidem or placebo. The primary outcome was suicidal ideation, measured with the SSI. Secondary outcomes included insomnia and depression severity.

Results: Patients had a mean baseline SSI score of 12, indicating moderate suicidal symptoms, and 30% had a previous suicide attempt. The mean baseline HAM-D score was 29 and did not differ between treatment groups. At the 1-week assessment, insomnia severity was significantly improved in the zolpidem group (p=0.004). However, at study end improvement relative to the placebo group was significant only in patients with severe insomnia (p<0.001). After adjustment for baseline scores, history of suicide attempts, and other factors, patients in both groups had small but significant average improvements in suicidal ideation, but there was no advantage in the zolpidem group. At the end of treatment, 61% of zolpidem-treated patients and 57% of the placebo group had SSI scores of zero. HAM-D scores improved significantly in both groups, with no difference between them. Insomnia severity and suicidal ideation scores were correlated, even after adjusting for changes in depression severity. There were no reports of worsening suicidal ideation, suicide attempts, or serious drug-related adverse events in either group.

Discussion: The results indicate that for some patients with depression and suicidal ideation zolpidem can provide short-term insomnia relief, which could in turn improve suicidality, particularly when the insomnia is severe. However, SSRI monotherapy was also associated with some improvement in insomnia and suicidality, and routine use of hypnotics may not be necessary.

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

McCall W, Benca R, Rosenquist P, Youssef N, et al: Reducing suicidal ideation through insomnia treatment (REST-IT): a randomized controlled trial. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2019.19030267. From the Medical College of Georgia, Augusta; and other institutions. **Funded by the NIMH. Six of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; fluoxetine—*Prozac*; sertraline—*Zoloft*; zolpidem—*Ambien

***See Reference Guide.**

Antidepressants and Gestational Diabetes

In a cohort of pregnant women, antidepressant use was associated with increased risk of gestational diabetes. Risk increases were modest for most antidepressants and absent for SSRIs.

Methods: Data were collected from the ongoing Quebec Pregnancy Cohort between 1998 and 2015. The cohort included only women with singleton pregnancies and excluded those with preexisting or newly identified diabetes, those who had experienced previous gestational diabetes, and those who were overweight or obese before becoming pregnant. Antidepressant exposure was defined as having filled ≥1 prescription after the first day of pregnancy. Prescriptions filled

before the start of pregnancy that continued into the gestational period were also considered. Women who received a diagnosis of gestational diabetes after the 20th week of pregnancy were matched with 10 controls without the condition.

Results: Nearly 21,000 women with gestational diabetes were identified in the cohort—8.8% of all pregnancies, consistent with the prevalence of reported cases in Quebec. Of these women, 1152 (5.5%) were exposed to antidepressants during pregnancy, compared with 8589 of the nearly 210,000 controls (4.1%). After adjustment for confounders, antidepressants were linked with an increase in risk of gestational diabetes (odds ratio [OR],* 1.19). Risk was not associated with antidepressant use before the first day of gestation. Analysis of separate antidepressant classes found risk was increased with SNRIs (OR, 1.27), TCAs (OR, 1.47), and combined use of >1 antidepressant (OR, 1.38), but not with SSRIs. When individual agents were assessed, risk was increased with venlafaxine (OR, 1.27) and amitriptyline (OR, 1.52).

Discussion: This study suggests that at least some antidepressants increase risk of gestational diabetes. Possible mechanisms include weight gain, direct effects on pancreatic insulin secretion, or increasing cellular insulin resistance.

Dandjinou M, Sheehy O, Bérard A: Antidepressant use during pregnancy and the risk of gestational diabetes mellitus: a nested case-control study. *BMJ Open* 2019; doi 10.1136/bmjopen-2018-025908. From CHU Sainte-Justine; and the University of Montreal, Canada. **Funded by the Canadian Institutes of Health Research. One of 3 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline—*Elavil*; 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.

Network Meta-Analysis: A meta-analytic technique that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method allows simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

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.

Risk Ratio: 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.

Standardized Mean Difference: The difference between two normalized means. A value of 0–0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and >0.8 a large effect.

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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