

What Works for Depression? An Evidence-based Comparison of Treatment Options

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Agenda

- AHRQ and the Effective Health Care Program
- Second-Generation Antidepressants for Treating Adult Depression—An Update from Dr. Gartlehner
- Questions and Answers

Web Conference Logistics

- Audio lines have been muted to minimize background noise.
- To ask a question:
 - **Use the WebEx Q&A function:** You may ask a question for the presenter at any time. Questions will be answered midway through and at the very end of the presentation.
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- Let us know what you think! Complete the evaluation form at the conclusion of the presentation. Look for the “Evaluation” pop-up.

Agency for Healthcare Research and Quality (AHRQ)

- **Mission:** To improve the quality, safety, efficiency, and effectiveness of health care for all Americans
- Research: ~80 percent of AHRQ's budget is invested in grants and contracts focused on improving health care
- The AHRQ Effective Health Care Program (EHC):
 - Provides current, unbiased evidence on clinical effectiveness of health care interventions
 - Focuses on patient-centered outcomes
 - Helps consumers, providers, and policy-makers make informed choices
 - Does not make treatment recommendations
 - Long-term goal: Improve health care quality and patient health outcomes through informed decision making by patients, providers, and policymakers

What is Comparative Effectiveness Research (CER)?

- Comparative effectiveness research — a type of patient-centered outcomes research — compares drugs, medical devices, tests, surgeries, or ways to deliver health care, so that patients and their families can make more informed choices.
- Findings are descriptive, not prescriptive, and are intended as tools for informed decision making, not recommendations.
- Findings highlight current evidence about effectiveness, risks, and side effects.

Second-Generation Antidepressants for Treating Adult Depression—An Update



Funding Support and Disclaimer

- Funded by the Agency for Healthcare Research and Quality (AHRQ) through Contract No. 290-2007-10056-1 to RTI International
- This presentation is provided to assist in decisionmaking and should not be construed to represent clinical recommendations or guidelines.
- Gartlehner G, Hansen RA, Morgan LC, et al. AHRQ Comparative Effectiveness Review No. 46.
Available at: www.effectivehealthcare.ahrq.gov/secondgenantidep.cfm.

Outline of Presentation

- **Background**
- **Questions addressed in the CER on second-generation antidepressants for adults with depressive disorders:**
 - Overall comparative effectiveness of treatments
 - Treating patients with unresponsive or recurrent disease
 - Treating depression with accompanying symptoms
 - Comparative adverse effects
 - Effectiveness and adverse effects in different patient subpopulations
- **Clinical Implications and Conclusions**

Background: Burden of Disease

- Depressive disorders such as major depressive disorder (MDD), dysthymia, and subsyndromal depression are serious, disabling illnesses.
- MDD affects more than 16 percent of adults at some point during their lifetimes.
- In any given year, about 7% of the US population suffer from a depressive episode.
- Women are about twice as likely as men to develop a depressive disorder.
- In 2000, the economic burden of depressive disorders in the United States was estimated to be \$83.1 billion.

Antidepressants Sales in the United States

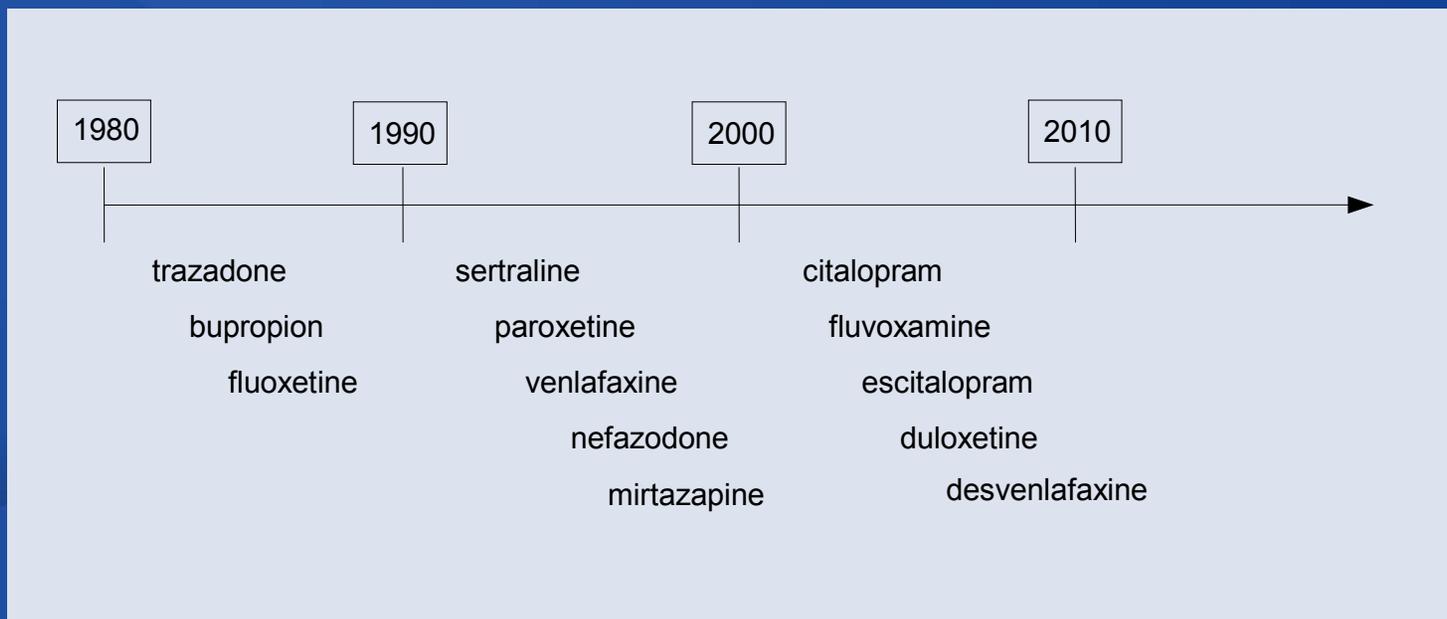
DISPENSED PRESCRIPTIONS MN		2011	2010	2009	2008
TOTAL US MARKET		4,024	3,993	3,949	3,866
1	Antidepressants	264	254	247	241
2	Lipid Regulators	260	260	254	242
3	Narcotic Analgesics	238	244	241	239
4	Antidiabetics	173	172	169	166
5	Ace Inhibitors (Plain & Combo)	164	168	166	163
6	Beta Blockers (Plain & Combo)	161	162	163	164
7	Respiratory Agents	153	153	152	147
8	Anti-Ulcerants	150	147	146	139
9	Diuretics	128	131	132	135
10	Anti-Epileptics	128	122	116	110

SPENDING \$ BN		2011	2010	2009	2008
TOTAL US MARKET		319.9	308.6	300.7	285.7
1	Oncologics	23.2	22.3	21.5	19.7
2	Respiratory Agents	21.0	19.3	18.1	16.0
3	Lipid Regulators	20.1	18.8	18.6	18.1
4	Antidiabetes	19.6	17.7	15.8	13.6
5	Antipsychotics	18.2	16.2	14.7	14.3
6	Autoimmune Diseases	12.0	10.6	9.7	8.6
7	Antidepressants	11.0	11.6	11.5	11.7
8	HIV Antivirals	10.3	9.3	8.2	7.1
9	Anti-Ulcerants	10.1	11.9	14.1	14.2
10	Narcotic Analgesics	8.3	8.4	8.0	7.3

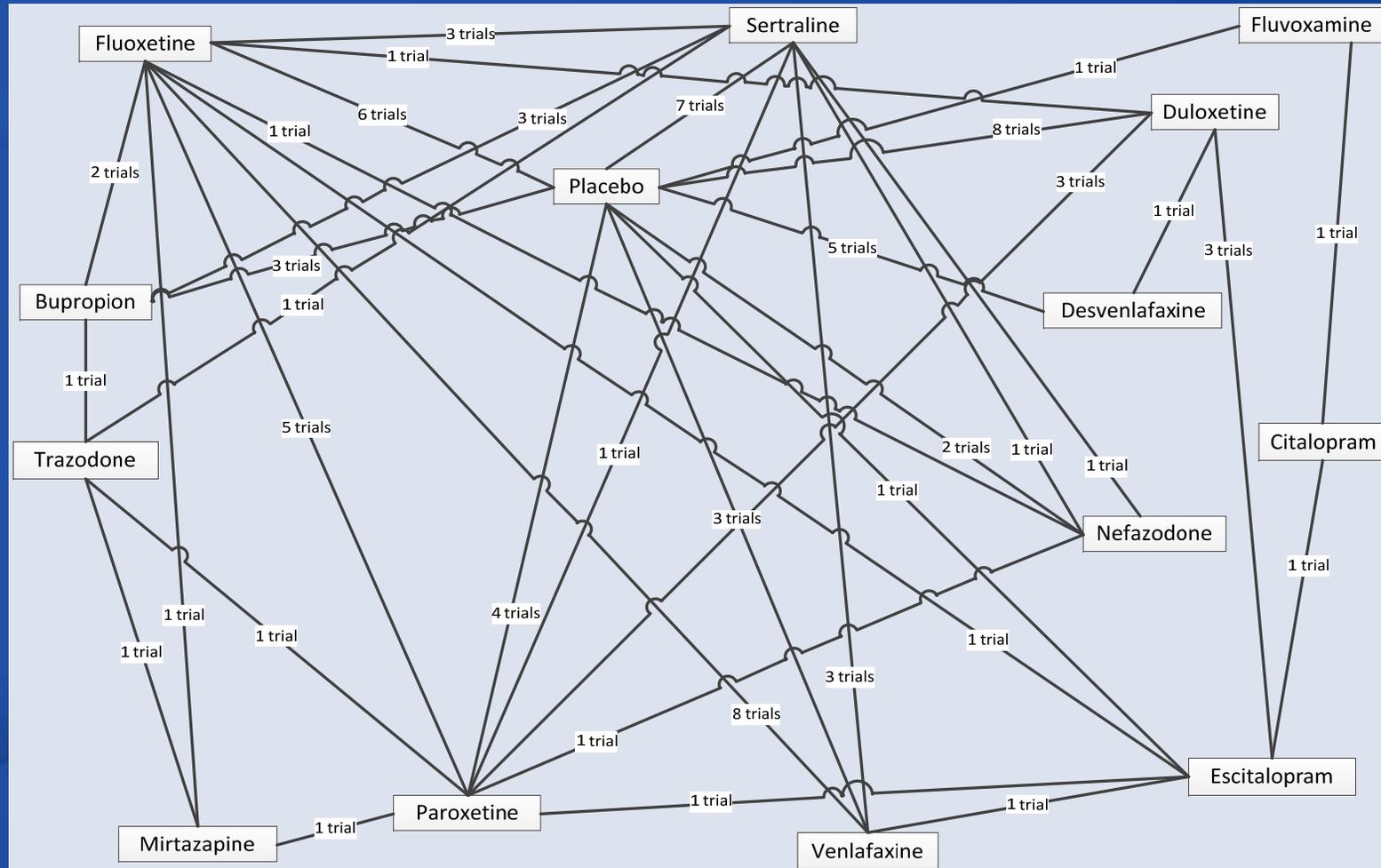
Source: IMS Health, National Sales Perspectives, Feb 2012

“Me-too” Drugs

- Drugs that are structurally very similar to already known drugs, with only minor differences.



Second-generation Antidepressants



Controversy about Comparative Effectiveness

CLINICAL GUIDELINES

Annals of Internal Medicine

Comparative Benefits and Harms of Second-Generation Antidepressants: Background Paper for the American College of Physicians

Gerald Gartlehner, MD, MPH; Bradley N. Gaynes, MD, MPH; Richard A. Hansen, PhD, RPh; Patricia Thieda, MA; Angela DeVeauugh-Geiss, MS; Erin E. Krebs, MD, MPH; Charity G. Moore, PhD, MSPH; Laura Morgan, MA; and Kathleen N. Lohr, PhD

...no substantial differences in efficacy among second-generation antidepressants

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Dr [Andrea Cipriani](#) PhD ^a , [Toshiaki A Furukawa](#) MD ^b, [Georgia Salanti](#) PhD ^c, [John R Geddes](#) MD ^d, [Julian PT Higgins](#) PhD ^e, [Rachel Churchill](#) PhD ^g, [Norio Watanabe](#) PhD ^b, [Atsuo Nakagawa](#) MD ^b, [Ichiro M Omori](#) PhD ^b, [Hugh McGuire](#) MA ^f, [Michele Tansella](#) MD ^a, [Corrado Barbui](#) MD ^a

....escitalopram and sertraline have a more beneficial efficacy/harms profile than other antidepressants.



Effective Health Care Program

Comparative Effectiveness Review
Number 46

Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review



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Effective Health Care Program

Medicines for Treating Depression

A Review of the Research for Adults



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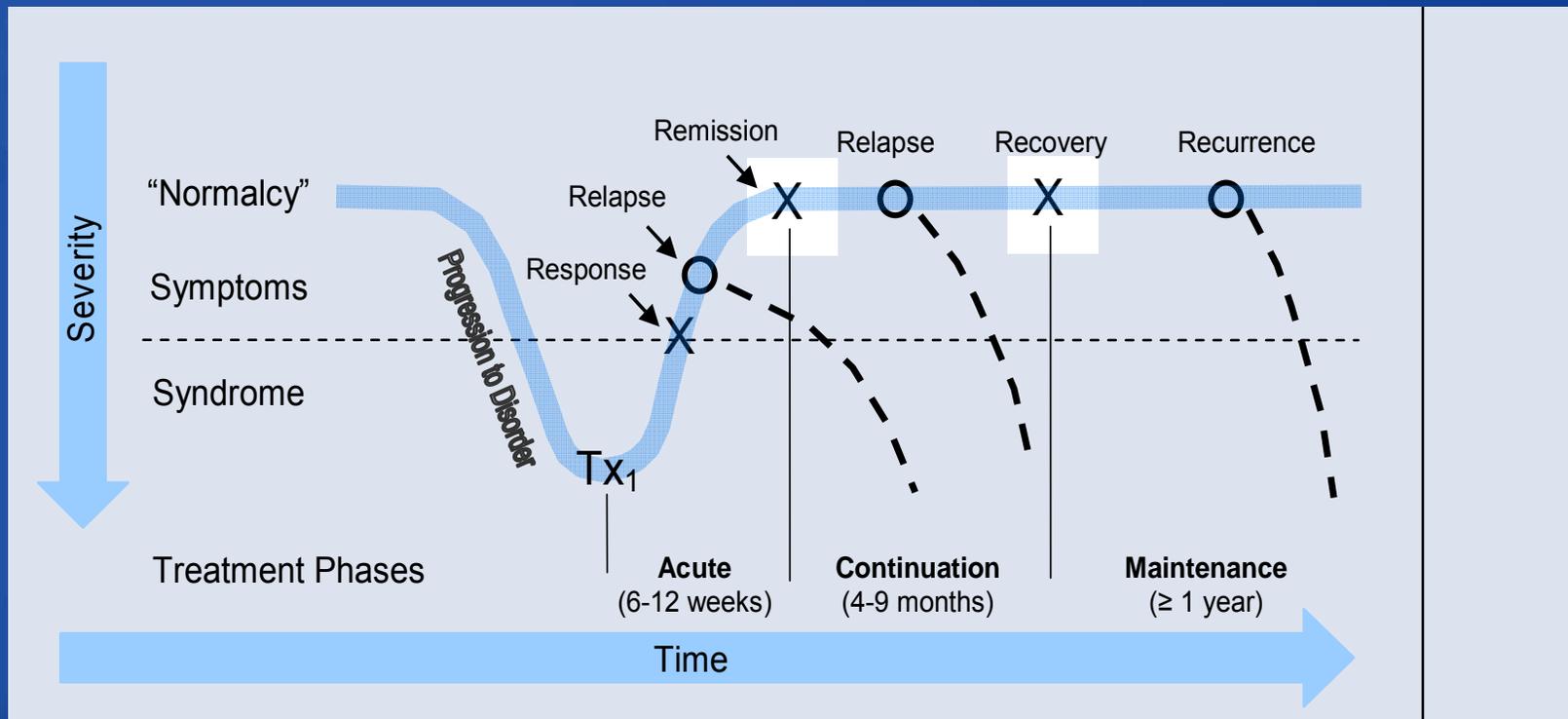
Effective Health Care Program

Population of interest

Adult outpatients with

- Major depressive disorder
- Dysthymia
- Subsyndromal depression

Phases of Treatment for Major Depression



Source: Recreated based on Kupfer, 1991

Second-Generation Antidepressants Included in the 2011 Updated Review

Generic Name	U.S. Trade Name ^a	Labeled Uses ^b	Therapeutic Classification
Bupropion ^c	Wellbutrin [®] ; Wellbutrin SR [®] ; Wellbutrin XL [®]	MDD; seasonal affective disorder	Other
Citalopram ^c	Celexa [®]	MDD	SSRI
Desvenlafaxine ^d	Pristiq [®]	MDD	SNRI
Duloxetine	Cymbalta [®]	MDD; GAD; neuropathic pain; fibromyalgia	SSNRI
Escitalopram	Lexapro [®]	MDD; GAD	SSRI
Fluoxetine ^c	Prozac [®] ; Prozac Weekly [®]	MDD; OCD; PMDD; panic disorder; bulimia nervosa	SSRI
Fluvoxamine ^c	Luvox [®]	OCD	SSRI
Mirtazapine ^c	Remeron [®] ; Remeron SolTab [®]	MDD	Other
Nefazodone ^c	Serzone ^{®e}	MDD	Other
Paroxetine ^c	Paxil [®] ; Paxil CR ^{®f}	MDD; OCD; panic disorder; social anxiety disorder; GAD; PTSD; PMDD ^f	SSRI
Sertraline ^c	Zoloft [®]	MDD; OCD; panic disorder; PTSD; PMDD; social anxiety disorder	SSRI
Trazodone ^c	Desyrel [®]	MDD	Other
Venlafaxine ^c	Effexor [®] ; Effexor XR [®]	MDD; GAD; ^g panic disorder; social anxiety disorder ^g	SNRI

^a CR = controlled release; SR = sustained release; XL or XR = extended release
^b GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor
^c A generic is available for some dosage forms.
^d Desvenlafaxine was not included in the 2007 report but is included in the 2011 updated review.
^e Only generic nefazodone is available in the United States.
^f Only Paxil CR (not Paxil) is approved for treating PMDD.
^g Only Effexor XR (not Effexor) is approved for treating GAD and social anxiety disorder.

Methods

- Systematic literature search in multiple electronic databases (1980-2011)
- Extensive grey literature searches for unpublished studies
- Dual review of the literature
- Critical appraisal of the risk of bias of included studies.
- RCTs for efficacy and effectiveness, observational studies for harms
- Meta-analyses and network meta-analyses
- Grading of the strength of evidence with respect to important outcomes

Methods

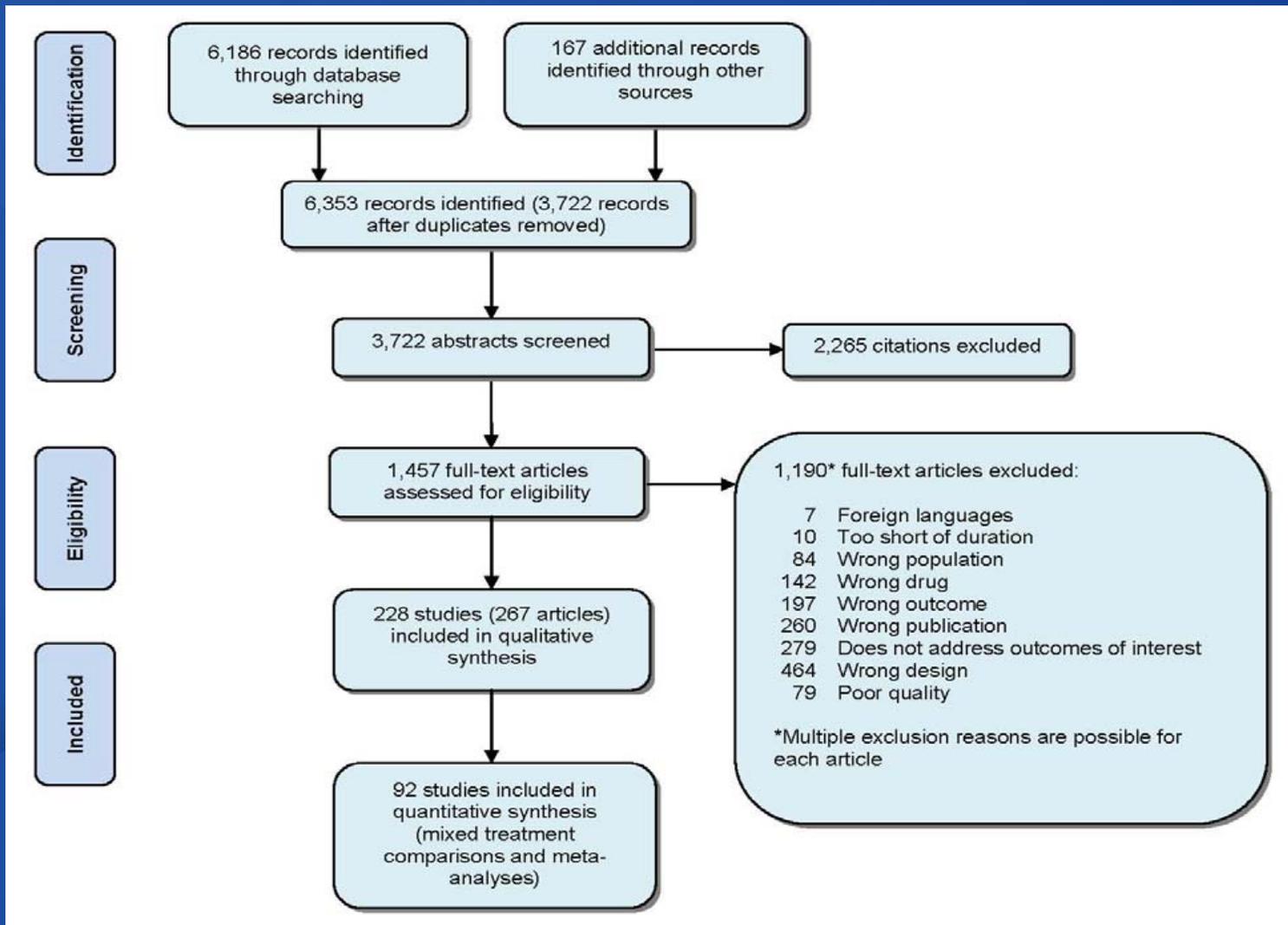
- The **strength of evidence** was classified into four broad categories:

High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Outcomes of Interest

Health Outcomes	Safety and Tolerability
<ul style="list-style-type: none">• Response• Remission• Speed of response/remission• Relapse• Quality of life• Functional capacity• Hospitalization	<ul style="list-style-type: none">• Overall adverse effects• Withdrawals• Serious adverse events• Specific adverse events including:<ul style="list-style-type: none">• Hyponatremia• Seizures• Suicide• Hepatotoxicity• Weight gain• Gastrointestinal symptoms• Sexual side effects• Others

Results



Results: Major Depressive Disorder

- 37% did not respond during 6 to 12 weeks of treatment; 53% did not achieve remission.
- The evidence is insufficient to determine factors that can reliably predict response or nonresponse in individual patients.

Results: Major Depressive Disorder

- Overall, similar efficacy, effectiveness, and effects on quality of life
 - Statistically significant differences are likely not clinically relevant
 - No differences between IR and XR formulations

Strength of Evidence: Moderate

- Mirtazapine has a faster onset of action (1–2 weeks) than citalopram, fluoxetine, paroxetine, and sertraline; Response rates were similar after 4 weeks of treatment.

Strength of Evidence: Moderate

Results: Major Depressive Disorder

- Overall, similar efficacy between immediate (IR)- and extended- release (XR) formulations
 - Fluoxetine daily vs. fluoxetine weekly
Strength of Evidence: Moderate
 - Paroxetine IR vs. paroxetine CR
Strength of Evidence: Moderate
 - Venlafaxine IR vs. venlafaxine XR
Strength of Evidence: Low
- Mixed evidence about better adherence and persistence with XR than IR medications
Strength of Evidence: Moderate to Low

Results: Preventing Relapse and Maintaining Remission

■ Maintaining Remission

- Most second-generation antidepressants effectively maintain remission (prevent relapse and recurrence) with similar efficacy.

Strength of Evidence: Moderate

Results: Achieving Response in Unresponsive or Recurrent Disease

■ Resistant or Refractory Depression

- Venlafaxine may be modestly superior to other selective serotonin reuptake inhibitors; however, results on comparative effectiveness are mixed.

Strength of Evidence: Low

QUESTIONS & ANSWERS



Treating Depression with Accompanying Symptoms

- Anxiety
- Insomnia
- Low Energy
- Melancholia
- Pain
- Psychomotor Change
- Somatization

Results: Treatment of Depression in Patients with Accompanying Symptom

- Similar efficacy for the treatment of depression in patients with accompanying symptoms

Strength of Evidence: Moderate (anxiety), low (insomnia), insufficient (low energy, melancholia, pain, psychomotor changes, somatization)

Results: Treatment of Accompanying Symptom in Patients with Depression

- Similar efficacy for the treatment of anxiety, pain, insomnia in patients with depression

Strength of Evidence: Moderate (anxiety, pain), low (insomnia)

- Insufficient evidence to determine the comparative efficacy of second-generation antidepressants in treating low energy, psychomotor changes, melancholia, or somatization.

Comparative Harms of Second-Generation Antidepressants

- Overall comparative risk of specific adverse events
- Discontinuation because of adverse events
- Risk of severe adverse events

Results: Risk of Harms

- Constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence were commonly and consistently reported adverse events.
- 63 percent of patients in efficacy trials experienced at least one adverse event.
- Nausea and vomiting were the most common reasons for discontinuation in efficacy studies

Results: Comparative Risk for Harms

- Overall rates of adverse events were similar among second-generation antidepressants, though incidence of specific adverse effects differed across antidepressants.
Strength of Evidence: High

Specific Comparative Harms of Second-Generation Antidepressants for Adults With MDD (1 of 3)

Adverse Effects	Outcome	Strength of Evidence
Nausea and Vomiting	<ul style="list-style-type: none"> • Venlafaxine has a 52-percent higher incidence than selective serotonin reuptake inhibitors as a class. 	High
	<ul style="list-style-type: none"> • When used to treat major depressive disorder, paroxetine IR may lead to higher rates of nausea than paroxetine CR. 	Low
Weight Gain	Mirtazapine is associated with more weight gain than citalopram, fluoxetine, paroxetine, and sertraline (0.8–3.0 kg after 6–8 weeks).	High
Diarrhea	Sertraline was associated with an 8-percent higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine.	Moderate

Specific Comparative Harms of Second-Generation Antidepressants for Adults With MDD (2 of 3)

Adverse Effects	Outcome	Strength of Evidence
Somnolence	Trazodone was associated with a 16-percent higher incidence of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.	Moderate
Sexual Dysfunction	<ul style="list-style-type: none"> Bupropion had fewer sexual side effects than escitalopram, fluoxetine, paroxetine, and sertraline. 	High
	<ul style="list-style-type: none"> Paroxetine had the highest rate of sexual side effects when compared with selective serotonin reuptake inhibitors as a class (16% vs. 6%). 	Moderate
	<ul style="list-style-type: none"> Sexual side effects may occur at different rates between men and women. 	Low

MDD = major depressive disorder

Specific Comparative Harms of Second-Generation Antidepressants for Adults With MDD (3 of 3)

Adverse Effects	Outcomes	Strength of Evidence
Discontinuation Rates	<ul style="list-style-type: none"> When compared with most SSRIs, higher discontinuation rates due to adverse effects were seen with duloxetine (67% higher risk) and venlafaxine (40% higher risk). 	High
	<ul style="list-style-type: none"> Venlafaxine had lower discontinuation rates due to lack of efficacy (35% lower risk). 	High
Withdrawal Symptoms	<ul style="list-style-type: none"> The highest rates of withdrawal symptoms (headache, dizziness, light-headedness, nausea, and anxiety) were reported after discontinuation of paroxetine or venlafaxine. 	Moderate
	<ul style="list-style-type: none"> Fluoxetine had the lowest rate of withdrawal symptoms. 	Moderate

MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor

Results: Serious Adverse Events

- The existing evidence on the comparative risk for rare but severe adverse events such as suicidality, seizures, cardiovascular events, hyponatremia, hepatotoxicity, and serotonin syndrome is insufficient to draw firm conclusions.

Results: Treating Depression in Subgroups

- Elderly patients (≥ 60 years) with MDD had similar efficacy with second-generation antidepressants.

Strength of Evidence: Moderate

- Elderly patients (≥ 60 years) with MDD may experience some differences in adverse events from these drugs.

Strength of Evidence: Low

Results: Treating Depression in Subgroups

- Insufficient evidence about differences in efficacy, effectiveness, or risk of harms for subgroups with respect to sex, race or ethnicities, and co-morbidities.

Results: Dysthymia and Subsyndromal Depression

- No double-blinded head-to-head evidence is available
- Evidence is limited to fluoxetine, paroxetine, and sertraline
- Evidence about the general efficacy of antidepressants for the treatment of dysthymia and subsyndromal depression is mixed.

Strength of Evidence: Insufficient (dysthymia) and low (subsyndromal depression)

Clinical Implications and Conclusions

- Current evidence does not warrant the choice of one drug over another based on efficacy.
- Although second-generation antidepressants are similar in efficacy, they cannot be considered identical drugs.
- Evidence of high and moderate strength supports some differences among individual drugs with respect to onset of action, adverse events, and some measures of health-related quality of life.

Clinical Implications and Conclusions

- Differences in adverse events or costs might influence the choice of a medication for an individual patient.
- Given the fact that almost two in five patients do not respond to initial treatment, clinicians need to be familiar with different antidepressants.

QUESTIONS & ANSWERS





Many thanks for your attention