

A Review of the Research Literature for Psychiatric Drug Withdrawal

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The image features a dark, star-filled space background with a prominent purple and blue nebula-like glow. In the center, there is a large black circle. Inside this circle, the text "Research on Psychiatric Drug Withdrawal" is written in a bold, orange-red font.

**Research on Psychiatric
Drug Withdrawal**

Withdrawal in the Research Literature

1. The Disease Model.

The drugs are treatments for a disease, and thus researchers study “relapse rates” when the drugs are withdrawn. The researchers are assessing the return of the illness in the absence of the treatment.

2. The Addiction Model

Psychotropic drugs are understood to induce compensatory adaptations in the brain, and thus withdrawal is understood to be a process involving the brain seeking to renormalize its neurotransmitter pathways (and other functions.)

3. The Lived Experience Model

Those who have sought to withdraw from their medications tell of their experiences, which may vary greatly from individual to individual.

The Disease Model

The Method

Researchers conduct randomized studies in patients who have stabilized on a drug (antipsychotic or antidepressant.) Patients are randomized either to placebo (withdrawal of the drug) or maintained on the drug, and then followed for a period of time.

The Outcome

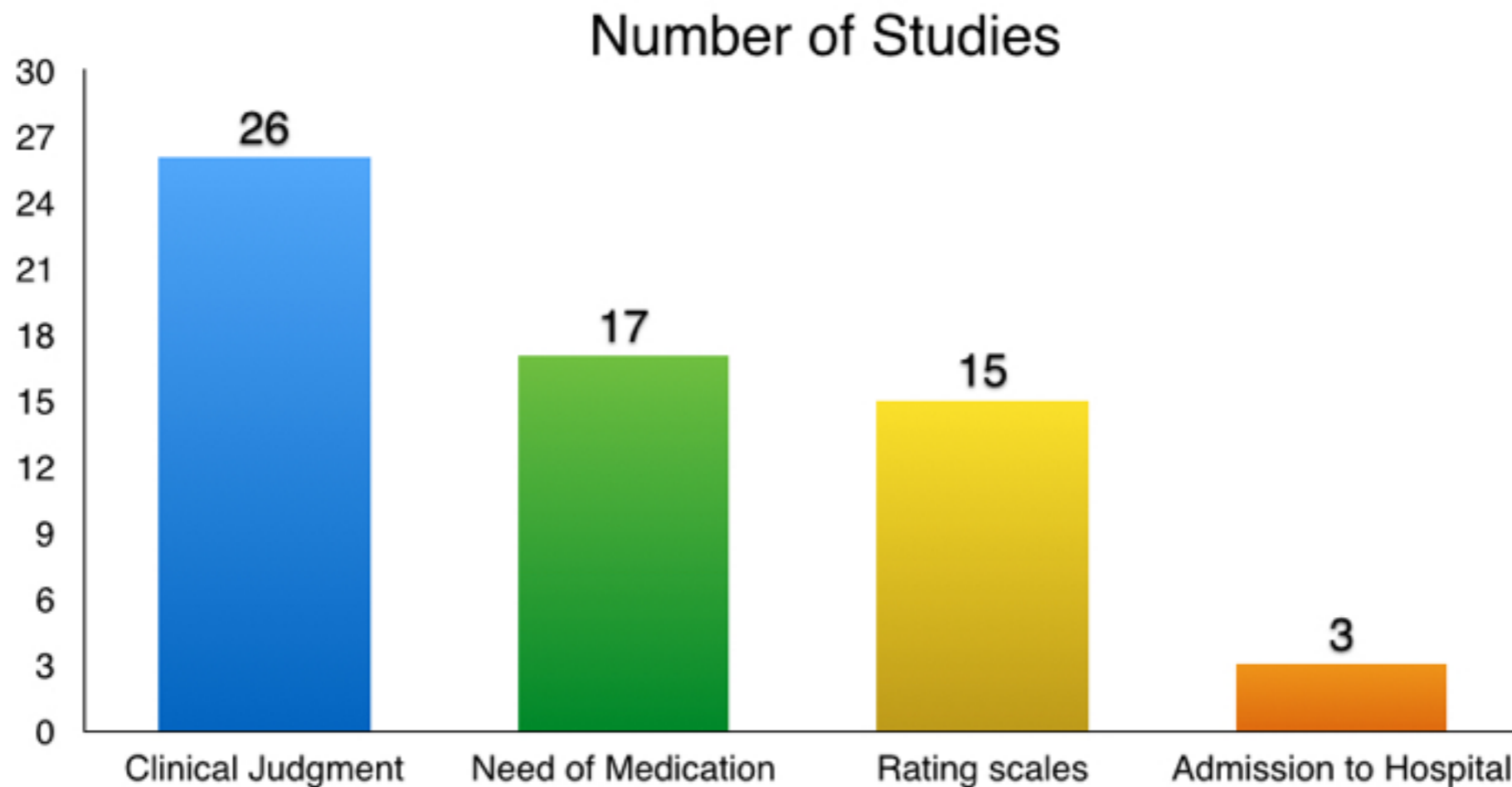
Researchers assess whether the target symptom returns (psychosis, depression, etc.), and if so, the patient is said to have “relapsed.”

The Interpretation

The fact that placebo patients “relapse” more frequently is taken as evidence that the drugs provide a long-term benefit, as they reduce the likelihood that the disease will return.

The Psychiatrist Determines Who Has Relapsed

In a 2012 review of 65 antipsychotic-withdrawal studies, here is how relapse was assessed:



Leucht, S. "Maintenance treatment with antipsychotic drugs for schizophrenia." Cochrane Database Review (2012), May 16.

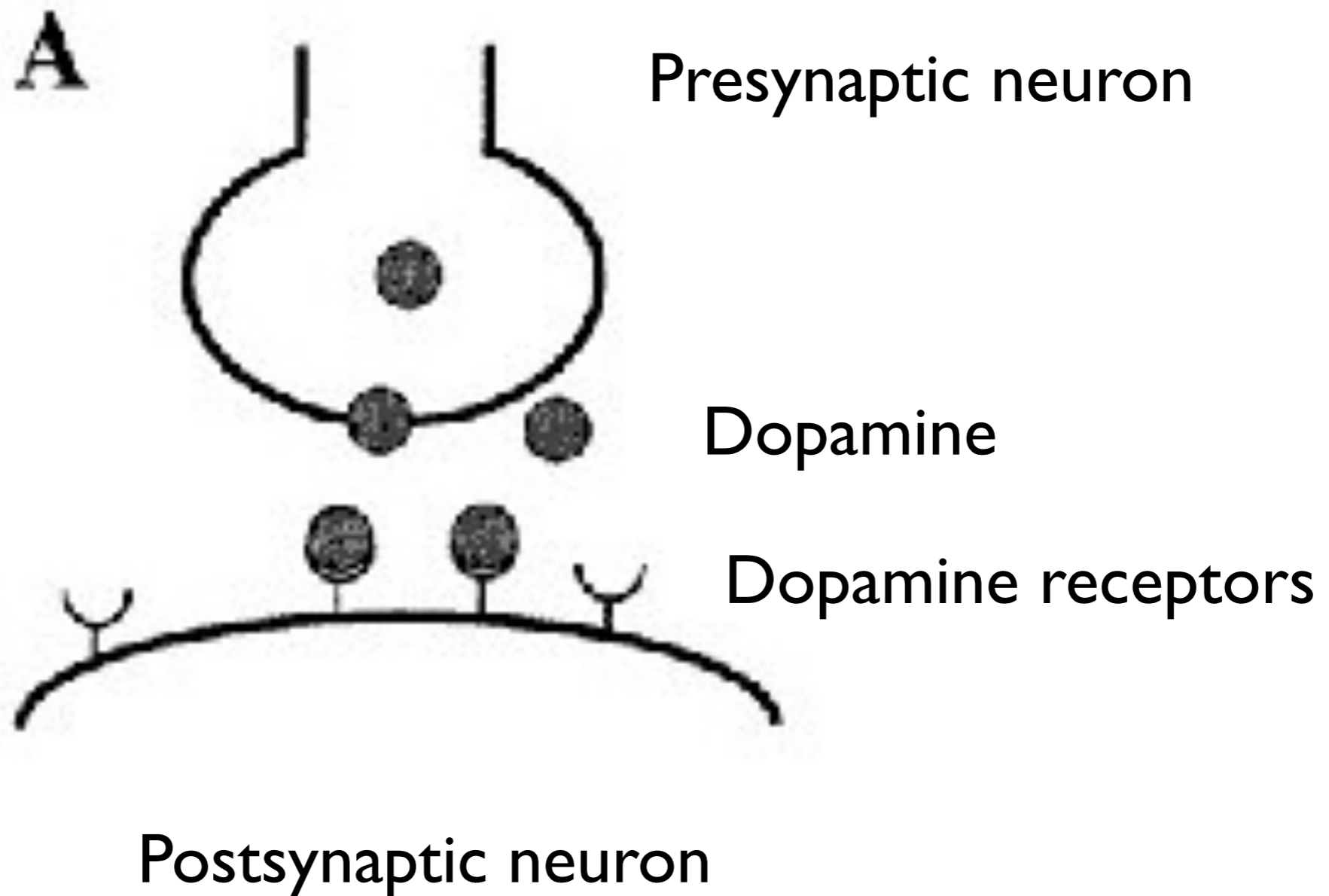
The Patient Experience in The Relapse Studies

- In 54 of the 65 studies, the antipsychotic was abruptly withdrawn.
- Only 3 of the 65 studies even assessed the patients' quality of life.
- Although “relapse” rates were lower in the drug-maintained group, 70% of this cohort either failed to improve or worsened during the study.
- In inpatient studies, only 5% of the drug-maintained patients were discharged.

The Addiction Model

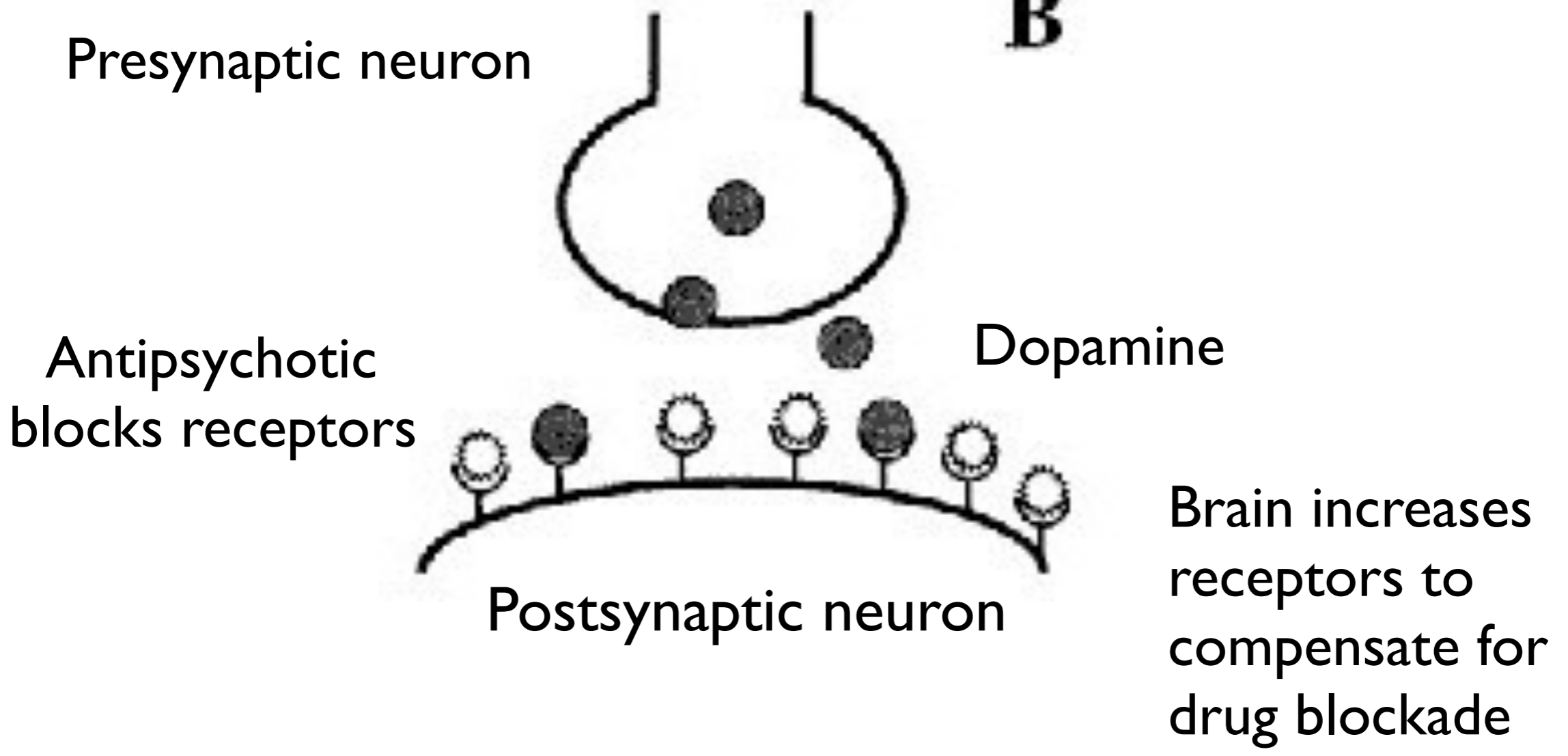
- Psychiatric drugs perturb neurotransmitter systems, which cause changes in receptor densities.
- During the withdrawal process, these receptor densities must renormalize, which may take an extended period of time.
- Withdrawal symptoms vary by receptor type, and half-life of drug.

Dopamine function before exposure to antipsychotics



Dopamine function after exposure to antipsychotics

B



Return of Symptoms May be a Withdrawal Symptom

“Long-term use of drugs that suppress certain neurotransmitters is thought to cause a compensatory increase in the number and/or sensitivity of the relevant receptors (the concept of supersensitivity). When these receptors are no longer opposed by drugs there is an over-activity of the neurotransmitter or systems involved. This may result in the characteristic discontinuation syndromes, may cause rapid onset psychosis [antipsychotic withdrawal] and may act as a source of ‘pharmacodynamic stress’ which increases vulnerability to relapse.”

—Joanna Moncrieff

Expected Effects From a Drug's Blockade of Receptors

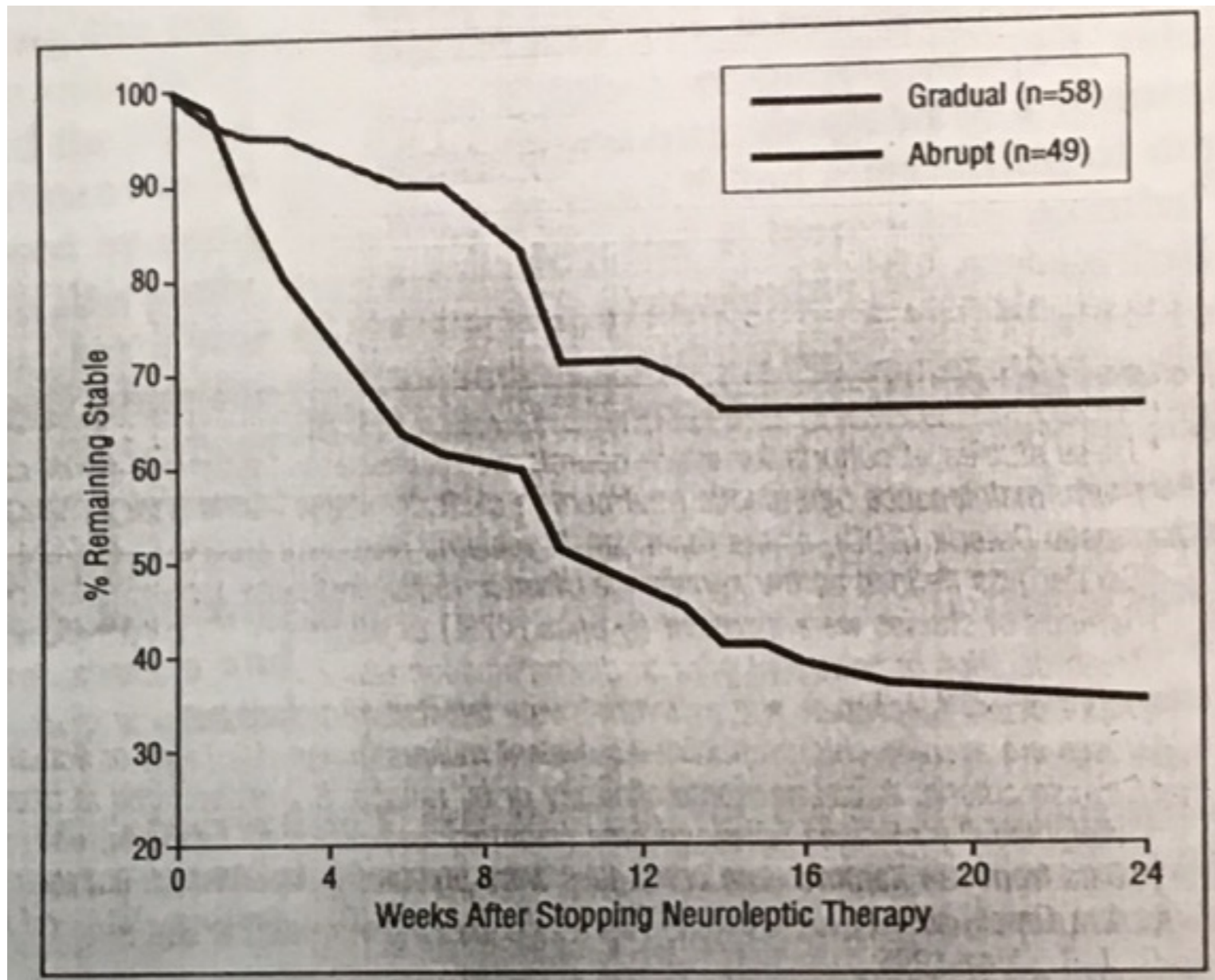
Receptor Type	Adverse Events	Withdrawal Effects
Dopamine	EPS, weight gain, endocrine effects, akathisia, tardive dyskinesia, increased prolactin, sexual or reproductive system dysfunction	Psychosis, mania, agitation, akathisia, dyskinesia
Serotonin	Weight gain, diabetes, increased appetite	EPS, akathisia, psychosis, decreased appetite
Histamine	Weight gain, diabetes, sedation	Agitation, insomnia, anxiety, EPS
Muscarinic	Dry mouth, blurred vision, constipation, urinary retention, diabetes, memory problems, cognitive problems, tachycardia, hypertension	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS, akathisia, diarrhea, nausea, vomiting, bradycardia, hypotension, syncope
Adrenergic	Postural hypotension, dizziness, syncope	Tachycardia, hypertension, hypotension, dizziness

EPS=extrapyramidal symptoms. Source: C Correll, "Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents." *J Clin Psychiatry* 69, suppl. 4 (2008): 26-36. Also see C. Correll, "Antipsychotic use in children and adolescents." *J Am Acad Child Adolesc Psychiatry* 47 (2008):9-20.

Gradual vs Abrupt Withdrawal

The understanding is that with gradual withdrawal, the receptors will more gradually return to normal densities, and that this will reduce the risk of relapse and the severity of withdrawal symptoms.

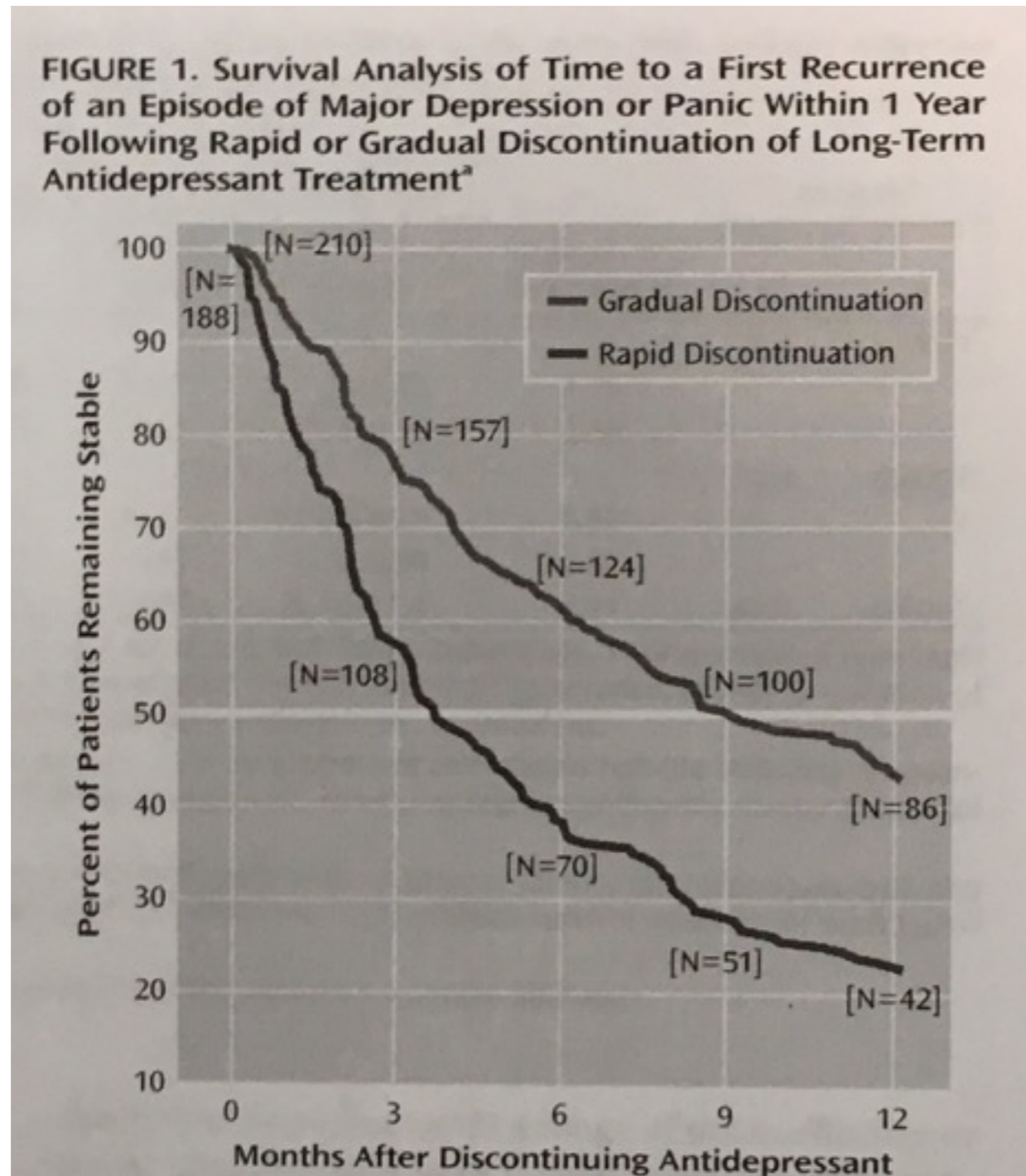
Relapse Rates Upon Withdrawal from Antipsychotics



Gradual= 3 weeks or longer,
or stopping of depot injection

Viguera, A. "Clinical Risk Following Abrupt and Gradual Withdrawal of Maintenance Neuroleptic Treatment." *Arch Gen Psychiatry* 54 (1997):49-55.,

Relapse Rates Upon Withdrawal from Antidepressants



Rapid = 1 - 7 days

Gradual = 14 days or more

But Do Receptor Densities Always Renormalize?

The case of TD

- Antipsychotics are known to cause tardive dyskinesia (TD.) The severity of this disorder has been found to associated with the increase of dopamine (D2) receptors (drug-induced dopamine supersensitivity.)
- Yet, in adults, TD regularly persists after the offending antipsychotic is withdrawn. Studies have found that D2 receptor levels remain abnormally high in such patients.

The case of PSSD

- SSRIs are known to cause sexual dysfunction or impairment in a high percentage of users of the drugs.
- In a significant percentage of patients, some degree of sexual dysfunction persists after drug withdrawal (PSSD).
- While the cause of PSSD is still unknown, one thought is that the down-regulation of serotonergic receptors persists “even after removal of the SSRI.”

Protracted benzodiazepine withdrawal syndromes

- Benzodiazepines induce a down-regulation of GABA receptors in the brain.
- GABA inhibits neural activity, and thus upon withdrawal, there is a deficiency in this “brake” upon normal neuronal activity.
- The fact that some long-term users of benzodiazepines suffer “protracted (withdrawal) symptoms” is probably “due to the failure of the (GABA) receptors to return to their normal state.” — Heather Ashton

One Hypothesis Re Protracted Withdrawal Syndromes

- A psychiatric drug acts as an acute stressor, which induces a compensatory adaptation.
- The change in receptor densities shows that there has been a change in the expression of the gene that codes for the receptor protein. The neuron's production of the protein has been "reset."
- When a drug is gradually withdrawn, there is no stressor that induces the cell to reset its production of the receptor protein.

The Big Worry

“Continued drug treatment may induce processes that are the opposite of what the medication originally produced.” This may “cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible.”

-Rif El-Mallakh, University of Louisville, 2011

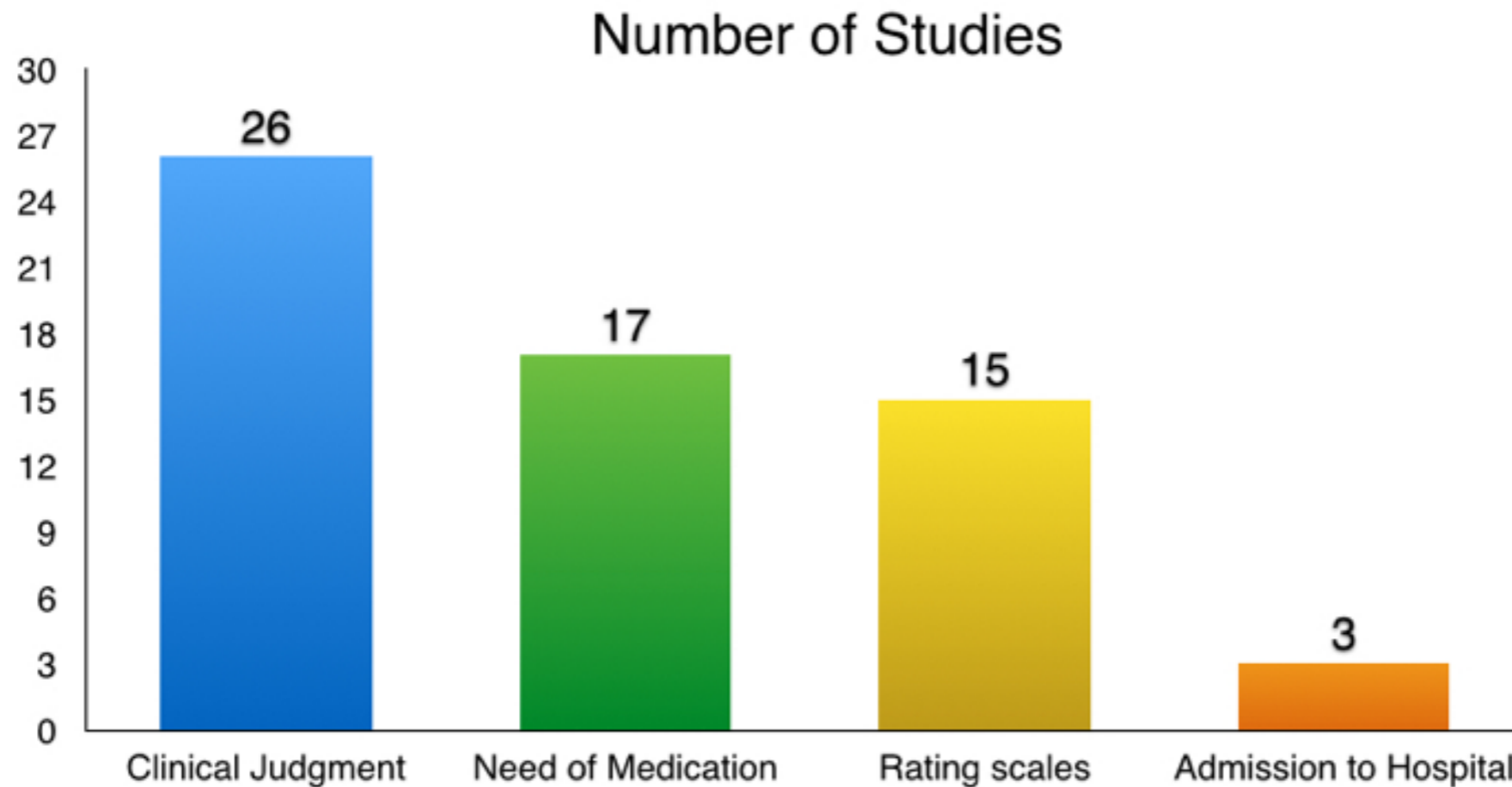
Source: El-Mallakh, R. “Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. *Medical Hypotheses* 76 (2011): 769-773.

Flaws with the Addiction Model

- Psychiatric drugs act on more than one receptor type.
- There are feedback loops in the brain that cause perturbations in one neurotransmitter system to cause changes in other neurotransmitter systems (such as the feedback loop between dopaminergic and serotonergic activity.)
- In the same class of drugs, individual drugs may have different binding profiles and varying half-lives, which lead to varying withdrawal symptoms.
- In the current era, patients often take several classes of psychiatric drugs, and there is no model that explains the physiology of brain changes caused by polypharmacy, or the possible renormalization of neurotransmitter systems following withdrawal from multiple drugs.

The Disease Model versus Addiction Model: Return of Illness or Withdrawal Symptoms?

In a 2012 review of 65 antipsychotic-withdrawal studies, here is how relapse was assessed:



Leucht, S. "Maintenance treatment with antipsychotic drugs for schizophrenia." Cochrane Database Review (2012), May 16.

A Proposed Model for Distinguishing Relapse from Withdrawal Symptoms

Withdrawal symptoms

- New symptoms common to withdrawal of CNS drugs.
- New symptoms common to withdrawal by receptor type.
- Rebound: return of original symptoms at greater intensity than original symptoms.
- Persistent post withdrawal disorders: Return of original symptoms at greater intensity or emergence of symptoms of new mental disorders.

Relapse/recurrence

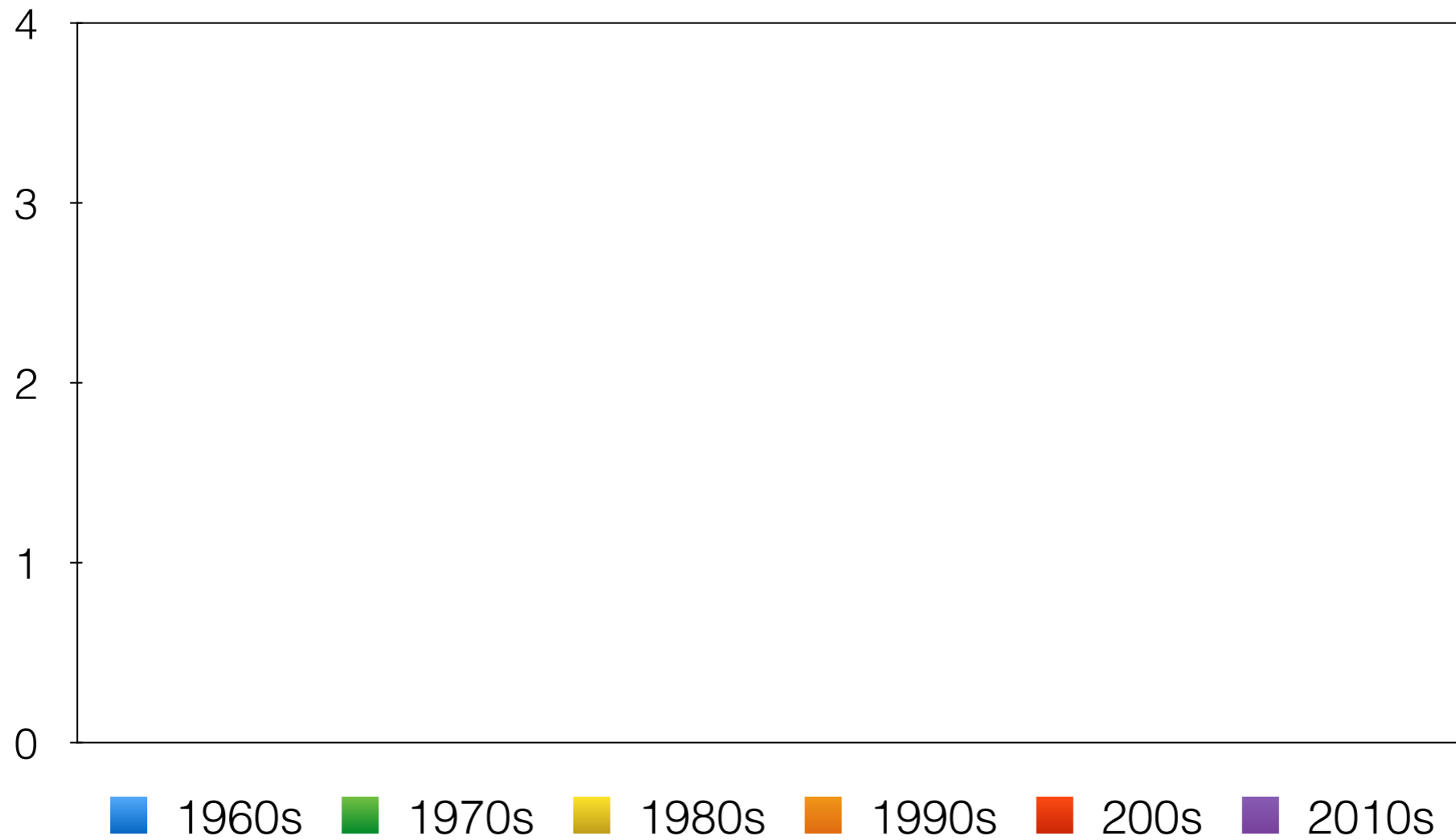
- Same episode returns; symptoms similar to original episode.

Withdrawal from Antidepressants

Withdrawal Symptoms	Relapse	Recurrence
New symptoms common to CNS drugs: nausea, headaches, sleep disturbances, anxiety, decreased concentration, agitation, dysphoria, aggression, depression. Symptoms appear within 36 to 96 hours, but may occur later. Last up to six weeks.	Same episode returns within 24 hours to six weeks.	New episode (following at least partial response to treatment.) Episode returns after six months or more.
Specific serotonin-related new symptoms: flu-like symptoms, dizziness, tachycardia, diarrhea, electric shock sensations, confusion, premature ejaculations. Symptoms appear within 36 to 96 hours, may last up to six weeks.		
Rebound: Return of original symptoms at greater intensity: anxiety, psychic anxiety, somatic anxiety, panic, agitation, insomnia, depression, dysphoria, obsessions, compulsions.		
Persistent post withdrawal disorders. Return of original symptoms at greater intensity and/or with additional symptoms. Appearance of symptoms related to emerging new mental disorders. Symptoms appear 24 hours to six weeks. May last several months or more.		

Chouinard, C. "New classification of selective serotonin reuptake inhibitor withdrawal." *Psychotherapy and Psychosomatics* 84 (2015): 63-71.

Number of Studies That Sought to Promote Successful Withdrawal from Antidepressants or Antipsychotics



A black hole with a glowing accretion disk and a starry background. The accretion disk is a bright, multi-layered ring of light surrounding the black hole, with colors ranging from white to purple. The background is a dark, starry space with a purple and blue nebula-like glow.

**Users' Accounts of
Withdrawal**

Why and How People Decide to Stop Taking Psych Drugs

A common reason often listed by psychiatry

- the patient lacks “insight” into his or her illness

What a survey of users’ found:

- they start taking the medication during a “major emotional crisis”
- the questioning of medications involves multiple steps:
 - the person experiences “losses generated” by taking the medication
 - questions the authenticity of their “self” on medication
 - feels their psychiatrist only cares about whether they are taking the medication
 - perception of “payoff matrix” changes; negative consequences seen as outweighing benefits
- there is a period of questioning: to “adhere or not to adhere”
- there is a gradual “resolving” of the conflict as the person becomes more determined and certain of his or her decision to stop, which is often keep “secret” from others
- they come to see this as a “personal issue,” of whether the meds are good for “them,” and making the choice to stop “contributes to their restoration of self”

Experiencing Antipsychotic Discontinuation: A Survey of Australian Consumers

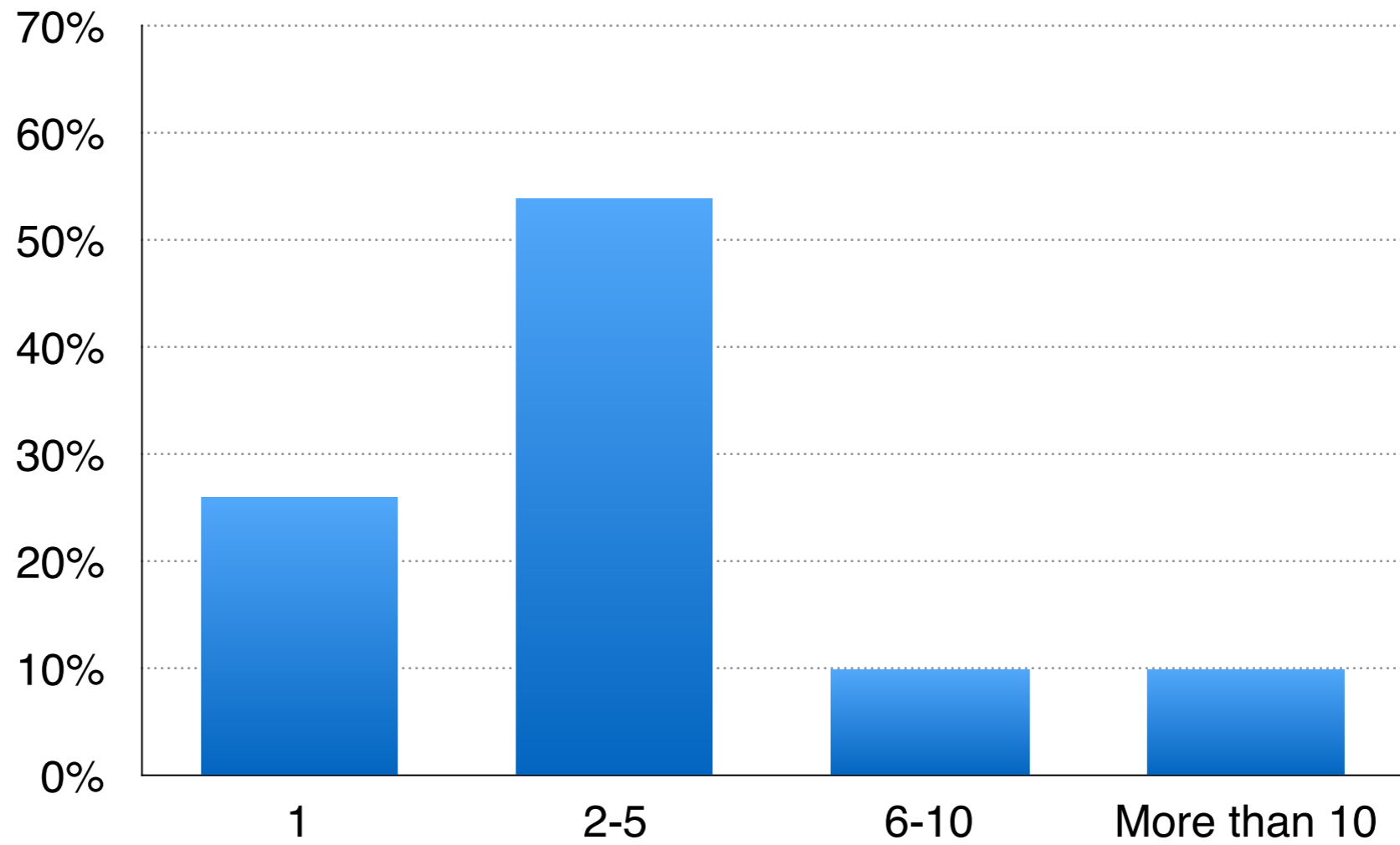
- Survey of 98 “consumers”, 88 of whom reported stopping an antipsychotic at least once.
- This (2014) study represents the “first investigation of Australian consumer perspectives on their antipsychotic discontinuation experiences.

Prescriber communications

- Nearly half of the sample (47%) reported they were not sure if their prescriber had given them any information about the proposed length of their antipsychotic treatment. Of those who did recall the topic being raised, 73% said they were told they would need to take an antipsychotic indefinitely or for life.
- Over half of the sample (56%) reported that they couldn't recall being given any information about what might happen if they discontinued their antipsychotic abruptly.
- Only 10 people reported that they were informed about the possibility of discontinuation symptoms others than relapse.

Number of discontinuation attempts

N = 88

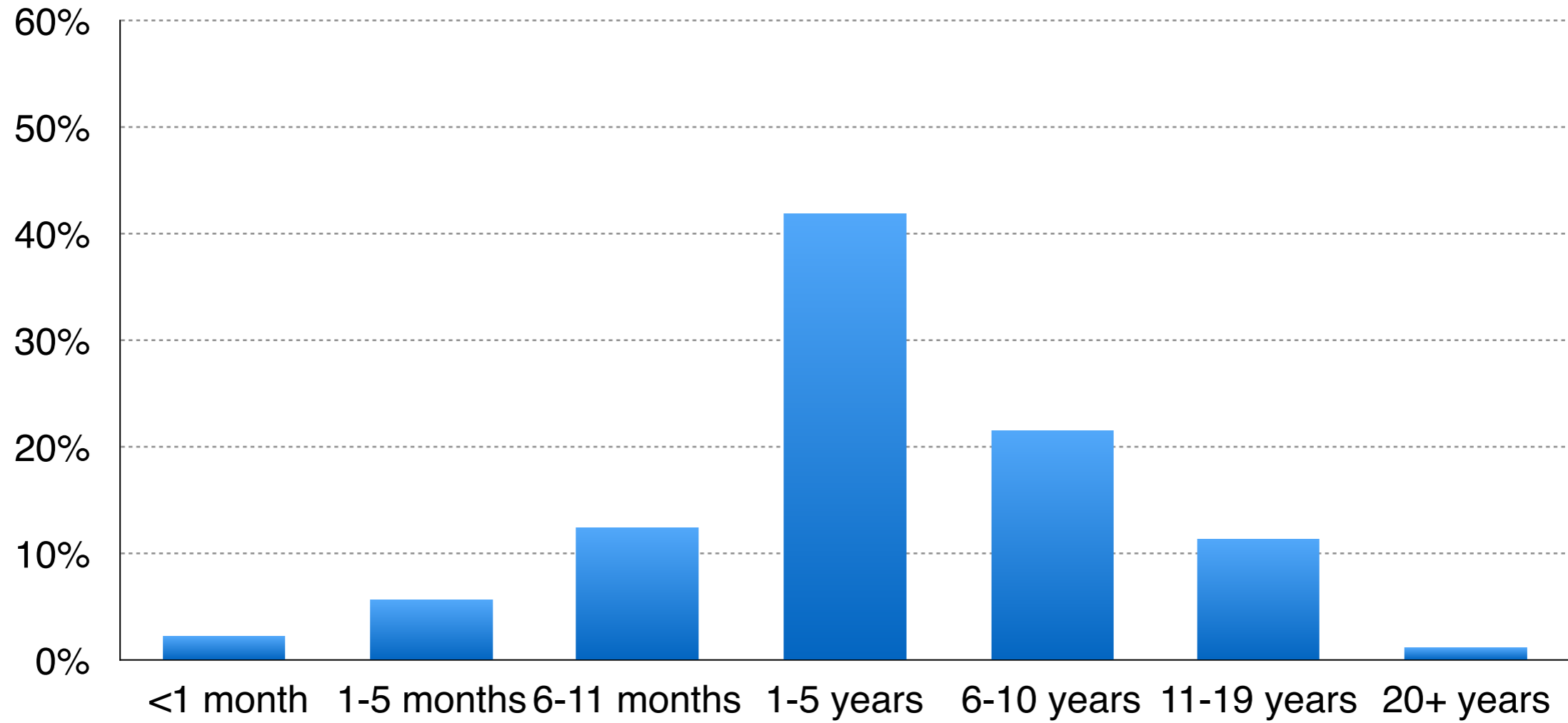


Reasons for stopping antipsychotic

- Didn't like adverse effects (54%)
- Didn't like idea of being on them long term (43%)
- Felt better and didn't need them (35%)
- The drug(s) were not useful (19%)
- Advised to come off them by doctor (19%)

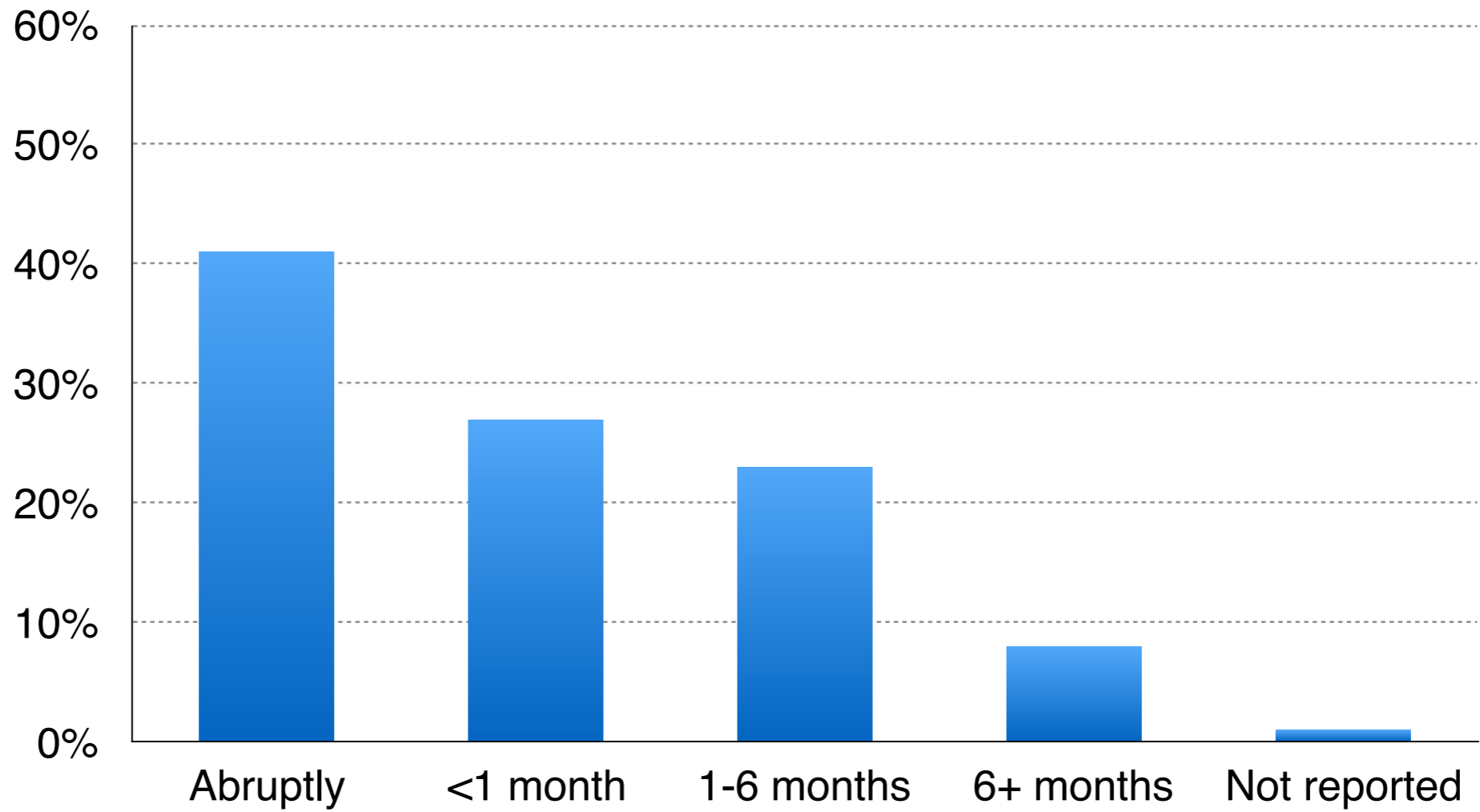
Length of time on antipsychotics before last discontinuation attempt

N = 88

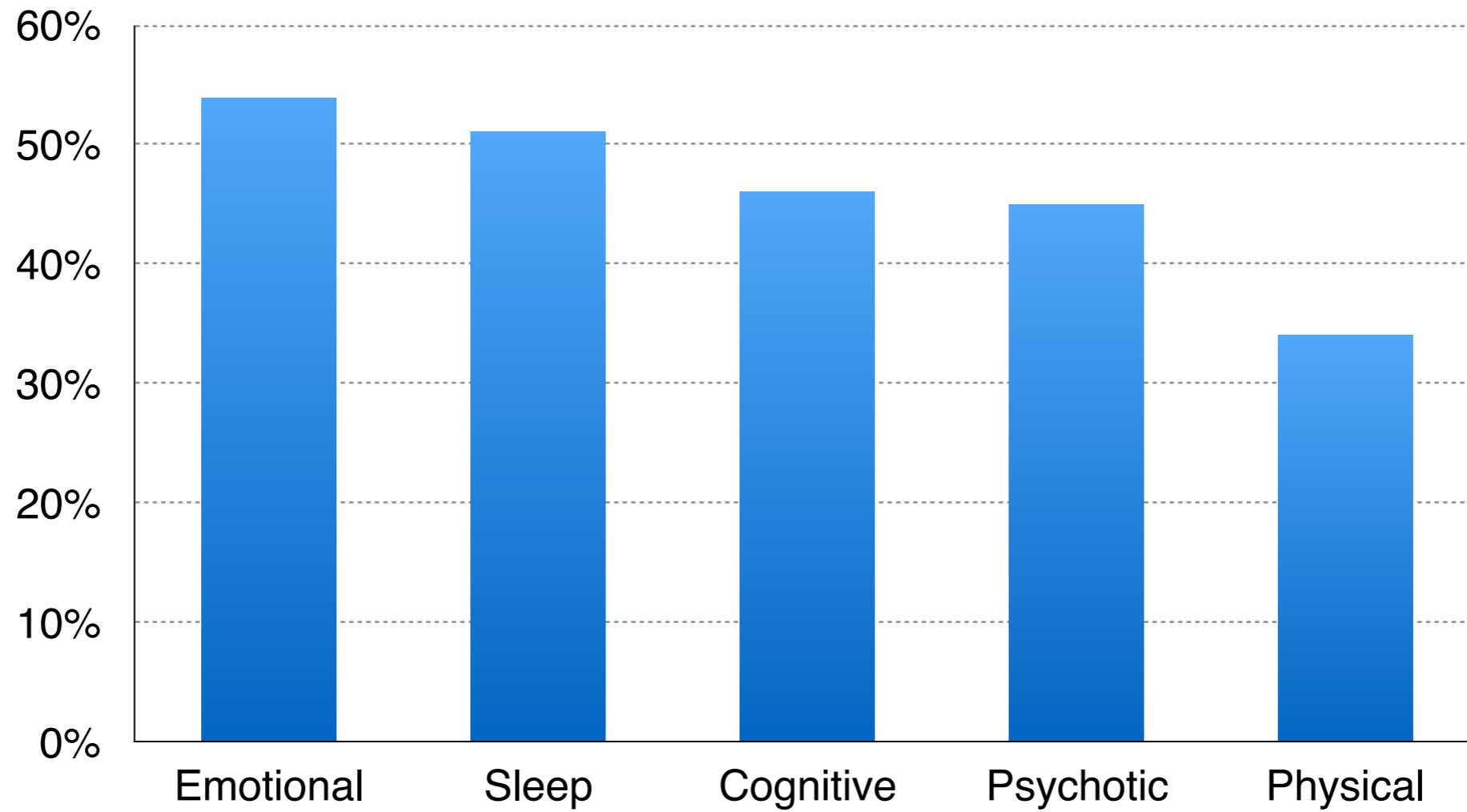


Speed of discontinuation

N = 88



Domains of reported discontinuation symptoms



Most common specific withdrawal symptoms

Difficulty falling asleep or staying asleep

Mood changes

Increase in anxiety/agitation

Increase in hallucinations/delusions/unusual beliefs

Difficulty concentrating/completing tasks

Increases in paranoia

Headaches

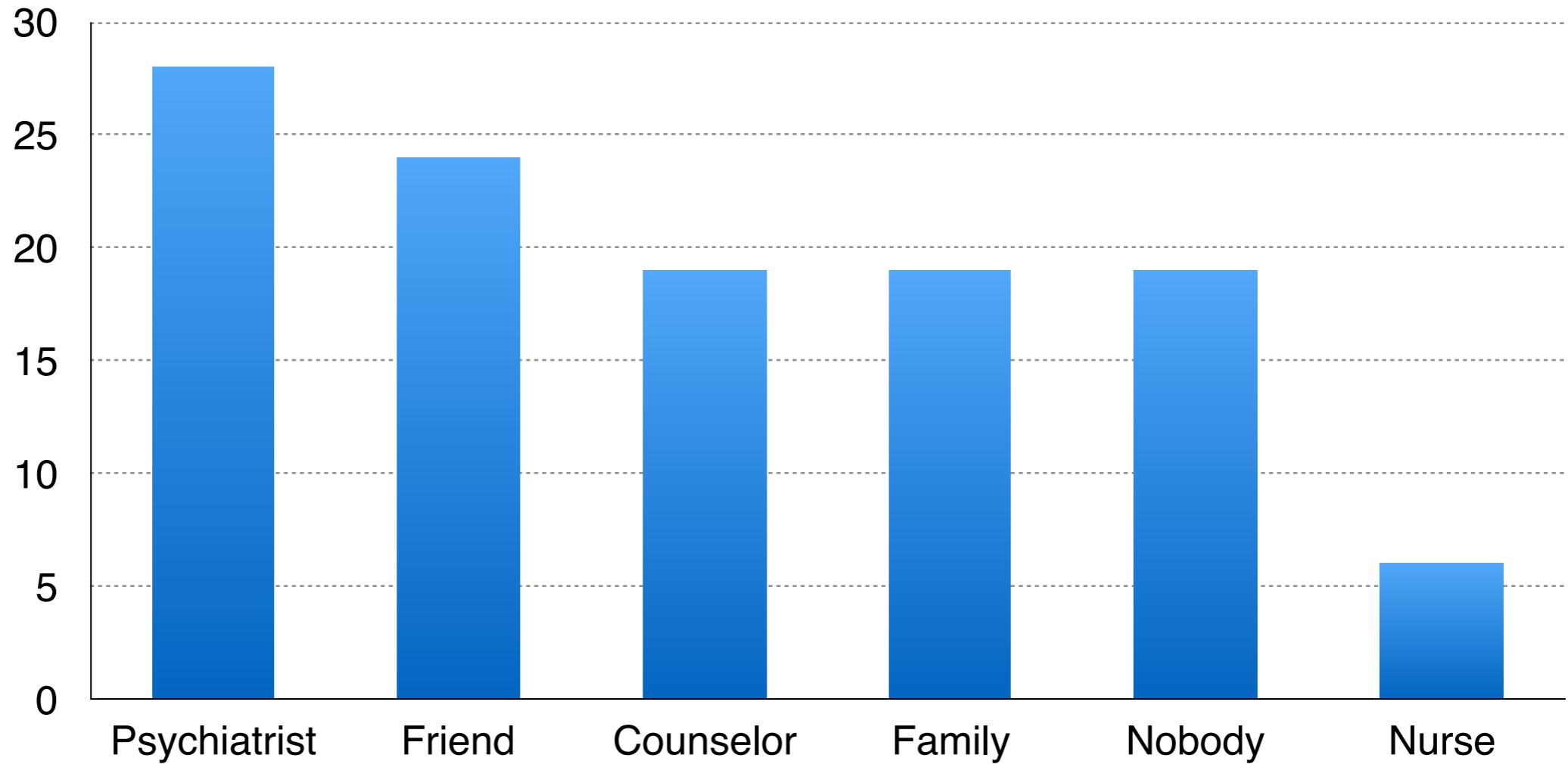
Memory loss

Nightmares

Nausea and vomiting

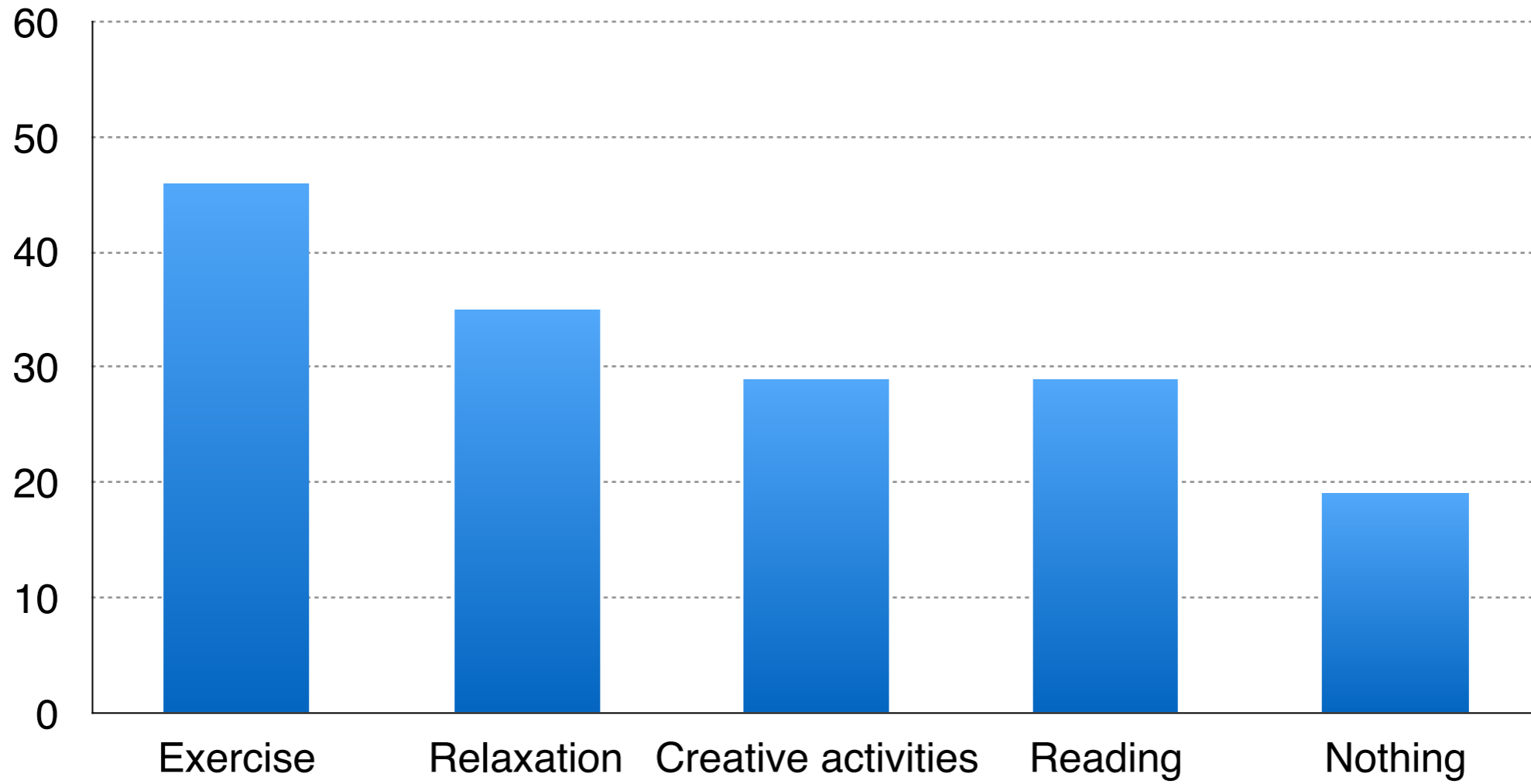
Most Helpful People

Number of
times named



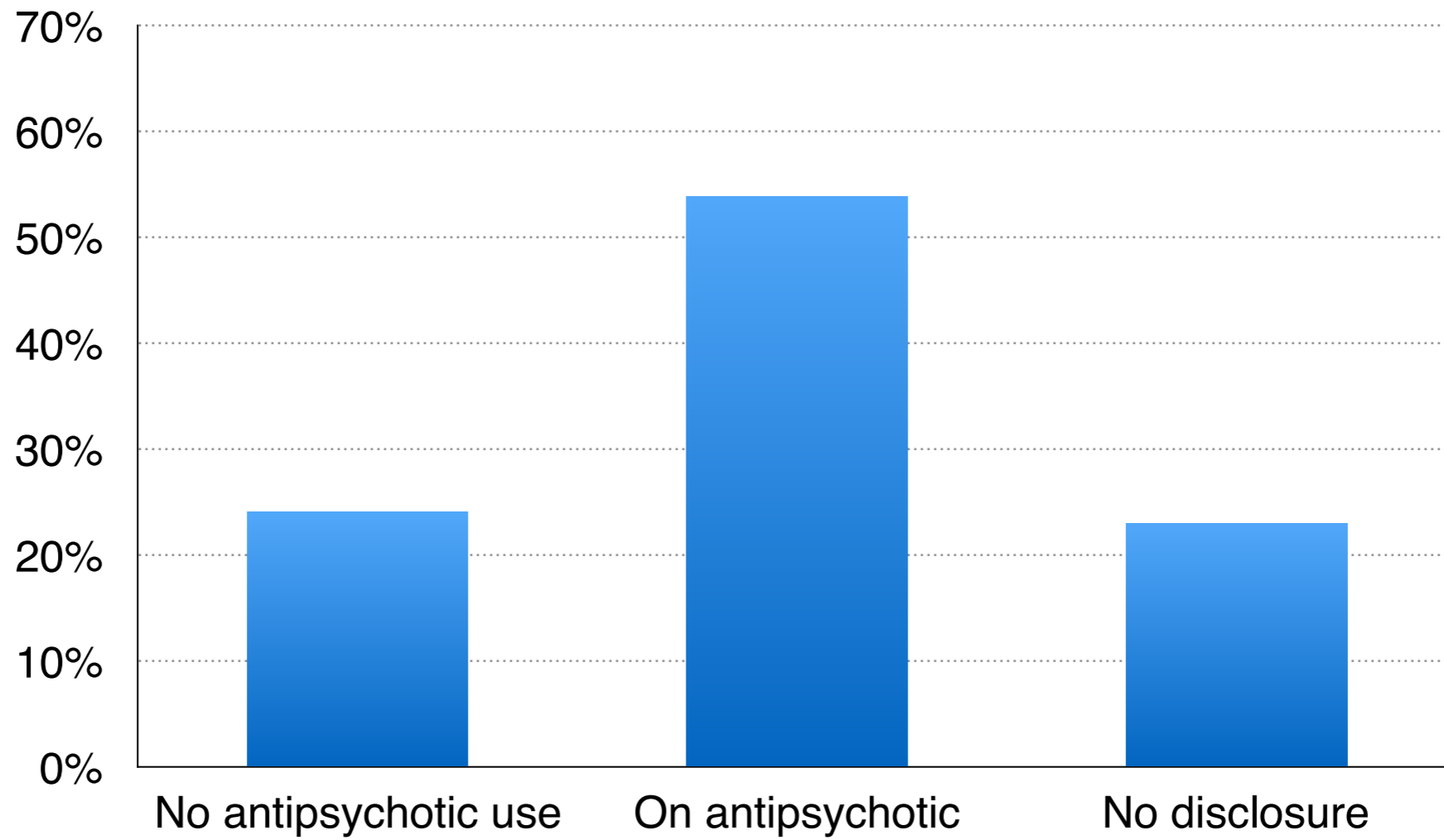
Helpful Activities

Number of
times named



Outcomes at time of survey

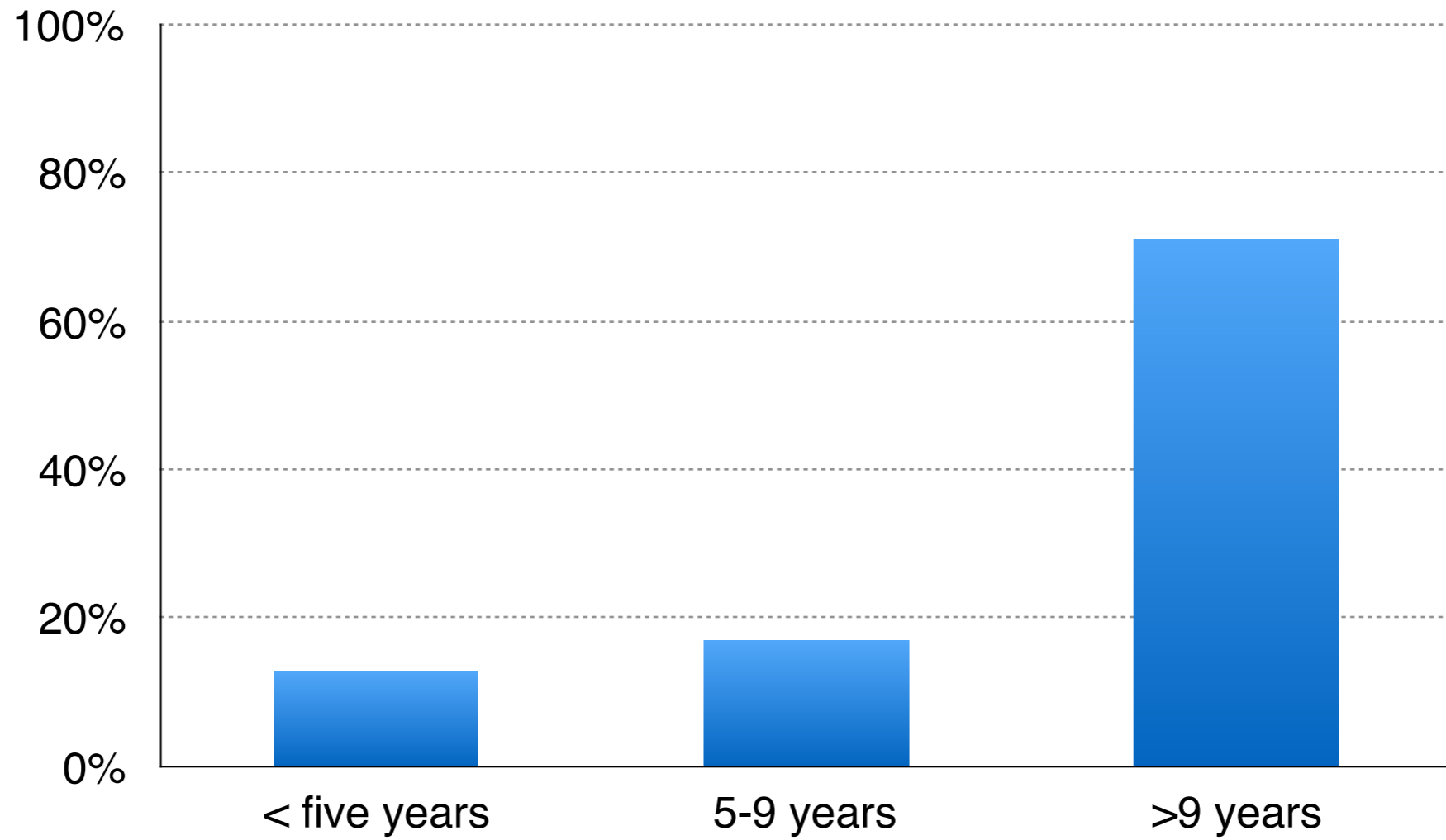
N = 88



Discontinuing Psychiatric Medications: A U.S. Survey

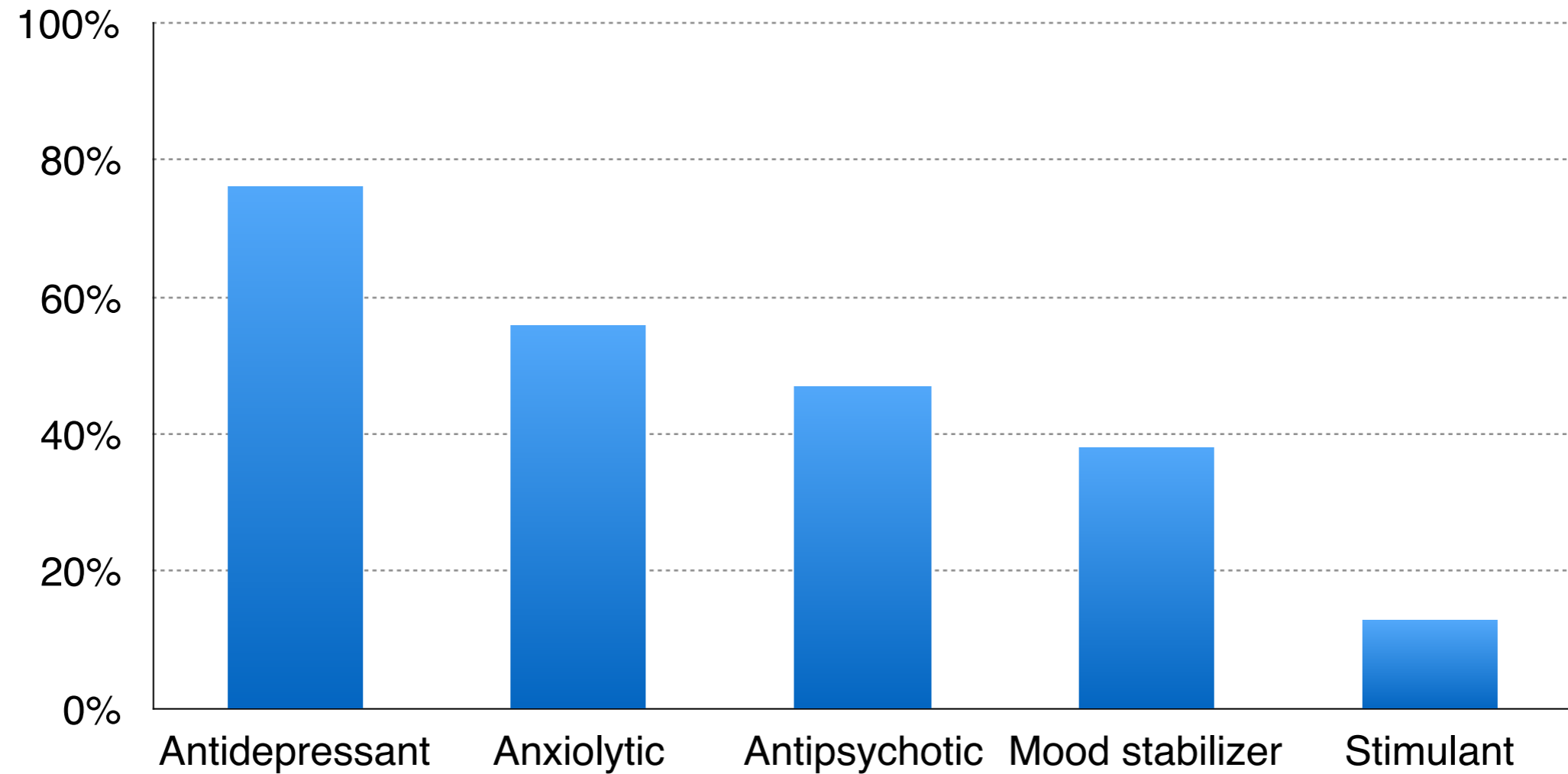
- Web survey of 250 people over age 18 with a diagnosis of a major mental disorder. All had taken one or more psychiatric medications for more than nine months in past five years, and had attempted to discontinue one or two of these medications.
- Diagnoses
 - 64% major depressive disorder
 - 41% bipolar disorder
 - 20% schizophrenia or other psychotic disorder

Total lifetime exposure to psychiatric medication

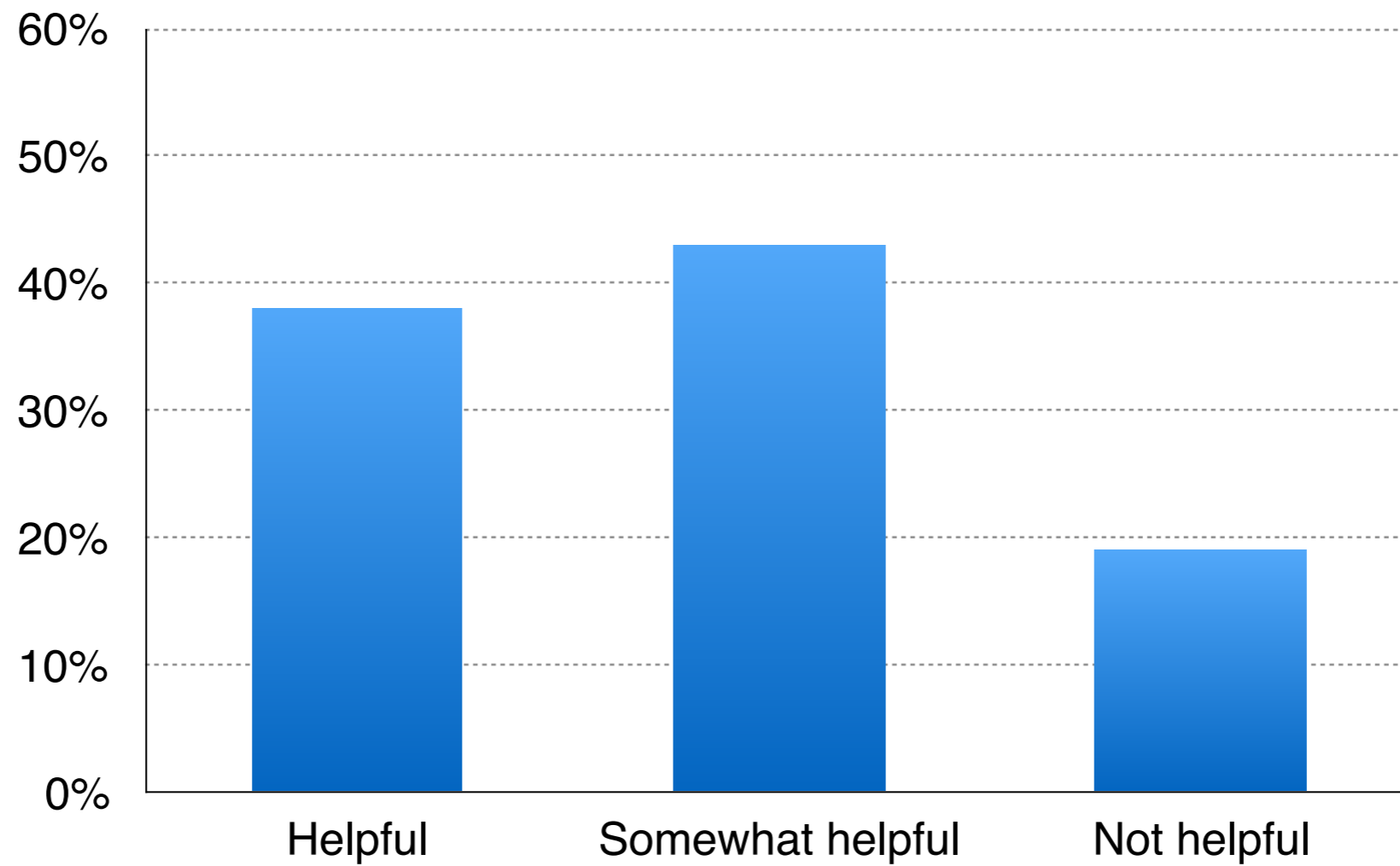


Class of psychiatric medication used before discontinuation

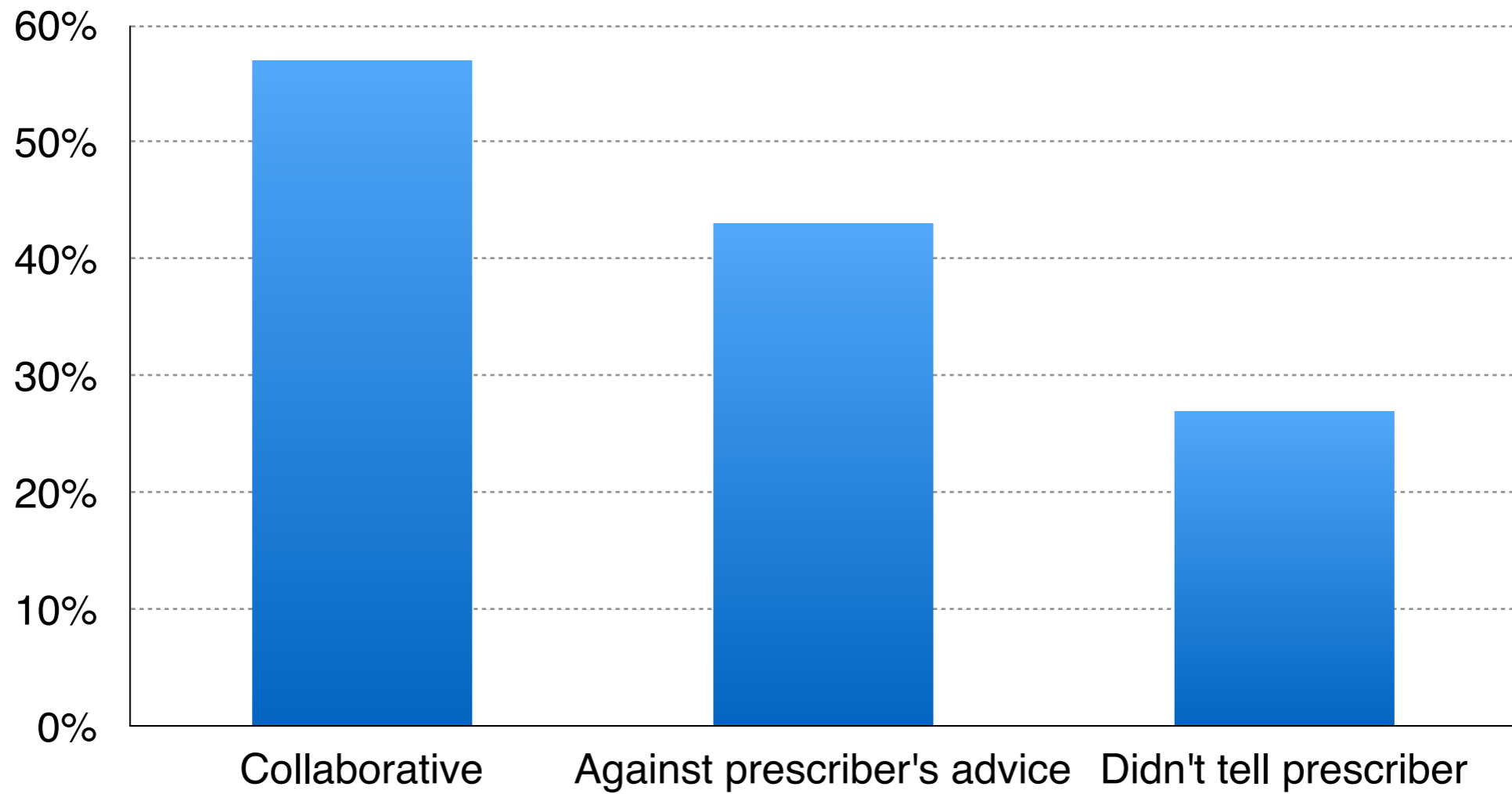
(For this study, max of 2 drugs)



Perceptions of medications before discontinuation



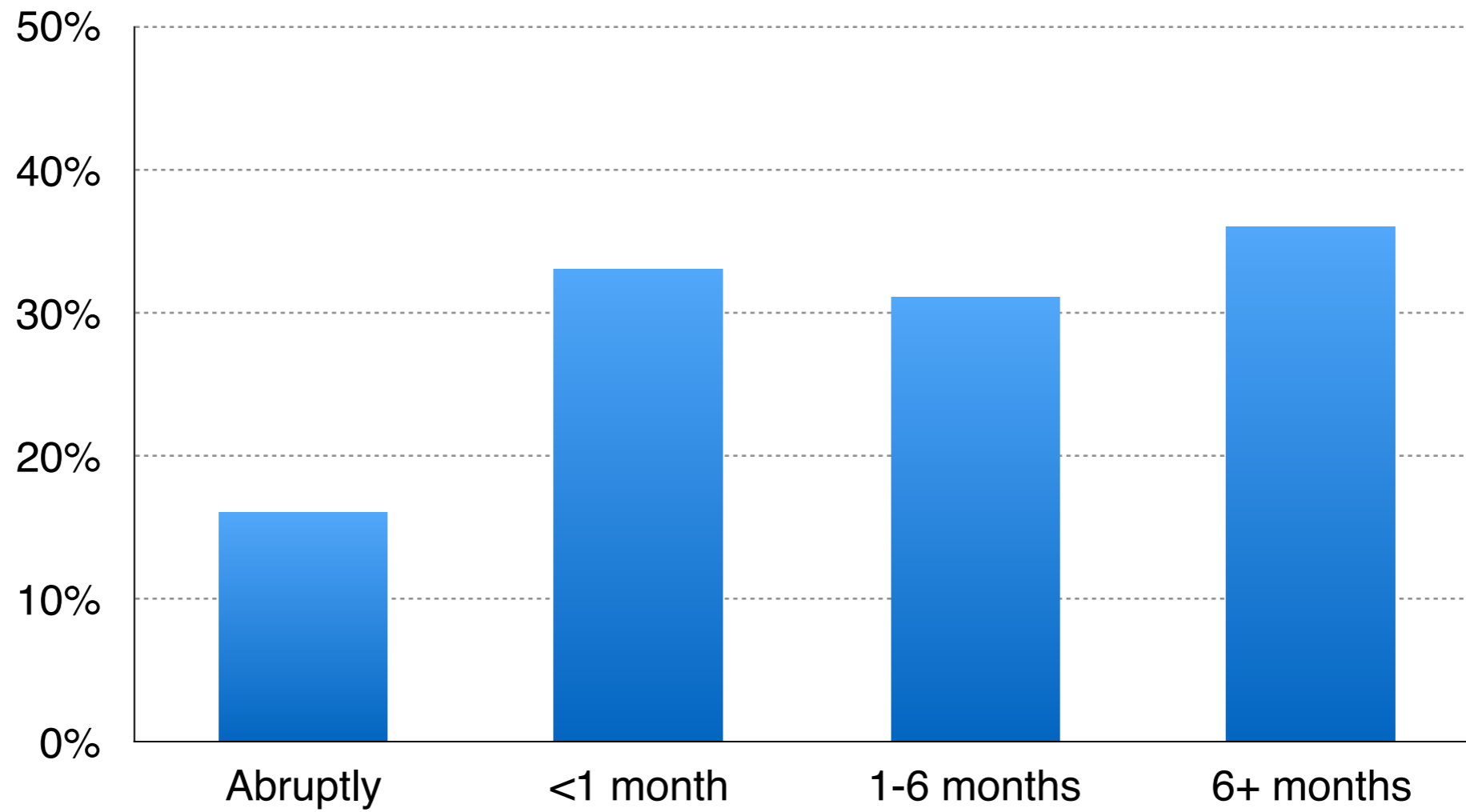
Provider support for discontinuation



Reasons for discontinuing psychiatric medications

Reason	%
Long-term effects	74
Adverse effects	73
Wanted to know who I am	48
Learned about alternative approach	34
Felt better	34
Drug not useful	29
Drug did not work anymore	23
Short term use intended	13
Concerned about reproductive health	13
Advised to discontinue by prescriber	8
Advised to discontinue by health care provider	5
No access to medications	4
Advised by someone in personal life	4
Other	29%

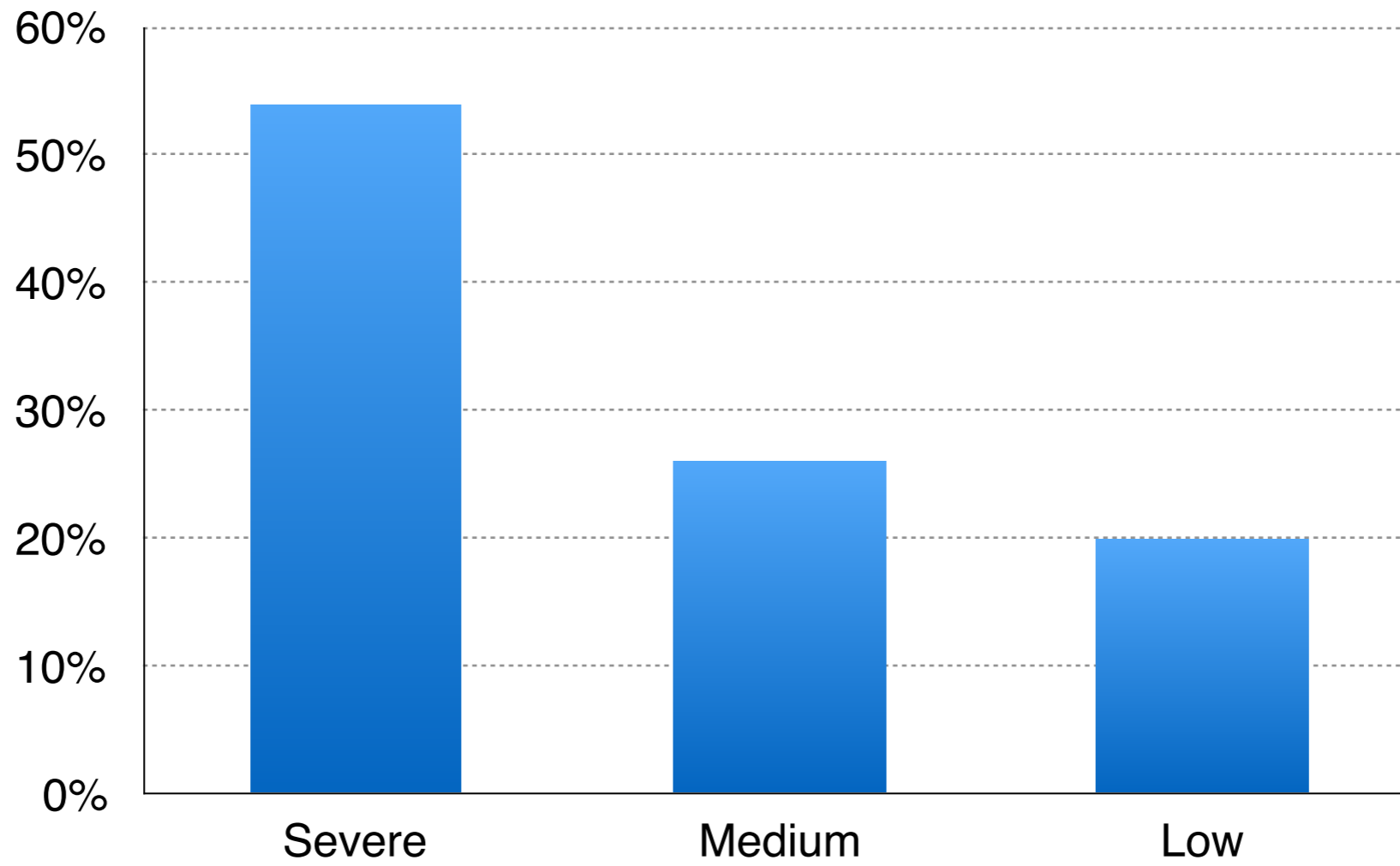
Speed of discontinuation



Withdrawal experiences

Effects	%
Sleep disruptions	80
Increased anxiety	76
Difficulty with emotions	73
Sadness, tearfulness	70
Fatigue	69
Difficulty with thinking	64
Flu-like symptoms	62
Difficulty with memory or concentration	61
Neurological symptoms (brain zaps, for example)	61
Diarrhea or constipation	47
Thoughts of suicide	44
Thoughts of self-harm	36
Psychosis	22%

Overall severity of withdrawal effects



Self-care coping strategies

Helpful practices used during discontinuation	%
Self-education about withdrawal	76
Outdoor activities	74
Getting sleep	67
Expressing feelings	67
Being with pets or animals	67%
Physical exercise	64

Outcomes

- 54% met their goal of completing discontinuing one or more medications.
- 82% of this group were satisfied or very satisfied with their decision to discontinue the medications.
- 46% either discontinued one medication but not the other; or remained on the same dose or higher.
- 50% of this group were satisfied or very satisfied with their decision to try to discontinue their medications.

Developing a Research Agenda

The disease model

In the absence of disease markers, which could be used to assess a return of the disease, should the relapse studies, which so often involved abrupt withdrawal of the drug, be seen as flawed and an invalid measurement of whether psychiatric drugs reduce symptoms over the long term?


The addiction model

- Do receptor densities renormalize? What is the speed at which this occurs?
- Is there renormalization of other domains (metabolic function, hormonal function, etc.)
- How does patient age and length of drug exposure affect renormalization/recovery processes?
- How does speed of drug withdrawal impact recovery processes?
- How does exposure to polypharmacy complicate recovery processes?
- Are there treatments that can promote recovery processes and lessen withdrawal symptoms?

The user-oriented model

- What are informational sources that can promote informed choices about whether to try a tapering/discontinuing effort?
- What are self-care strategies that can help lessen withdrawal symptoms: exercise, diet, sleep, and so forth?
- What are the social supports—support from providers, family, friends and peers—that can help people cope with withdrawal symptoms?

The Future?

A black hole with a central black circle containing text, surrounded by a glowing ring and a starry background.

**Psychiatry has
developed informed
protocols for drug
discontinuation**