Future directions in antidepressant pharmacotherapy

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I have no relevant financial relationships with commercial interests to disclose

Future directions

1. The current state of antidepressant treatment
2. A new framework for understanding depression
3. Novel pharmaceutical targets

Treatments for depression: Where are we today?

- Limited efficacy
- Slow onset of action
- Not all symptoms will respond

Current treatments have limited efficacy[1,2]

- STAR*D
- CO-MED

1. Warden D, Rush AJ, Trivedi MH, Fava M, and Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. *Mood Disorders.* 2007;9(6):449-459.
2. Rush AJ, Trivedi MH, Stewart JW, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry.* 2011;168(7):689-701.

Even when medications do work, it may take many weeks for symptoms to improve[1]

1. Murrough JW, and Charney DS. Is there anything really novel on the antidepressant horizon? *Curr Psychiatry Rep.* 2012;14(6):643-9.

Some symptoms – apathy, indifference, emotional numbing – can actually get worse with treatment[1, 2]

1. Hoehn-Saric R, Lipsey JR, and McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol.* 1990;10:343-45.
2. Sato S, and Asada T. Sertraline-induced apathy syndrome. *J Neuropsychiatry Clin Neurosci.* 2011;23(1):E19.

None of the five antidepressants approved by the FDA over the past decade has been meaningfully “new”

duloxetine	(8/2004)[1]	**SNRI**
desvenlafaxine	(2/2008)[2]	**SNRI**
vilazodone	(1/2011)[3]	**SARI**
levomilnacipran	(7/2013)[4]	**SNRI**
vortioxetine	(9/2013)[5]	**SARI**

1. Kirwin JL, and Gören JL. Duloxetine: a dual serotonin-norepinephrine reuptake inhibitor for treatment of major depressive disorder. *Pharmacotherapy.* 2005;25(3):396-410.
2. Yang LP, and Plosker GL. Desvenlafaxine extended release. *CNS drugs.* 2008;22(12):1061-1069.Laughren TP, Gobburu K, Temple RJ, et al. Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant. *J Clin Psychiatry.* 2011;72(09):1166-1173.
3. Saraceni MM, Venci JV, and Gandhi MA. Levomilnacipran (Fetzima): a new serotonin-norepinephrine reuptake inhibitor for the treatment of major depressive disorder. *J Pharm Pract.* 2013.
4. Gibb A, and Deeks ED. Vortioxetine: first global approval. *Drugs.* 2014;74(1):135-45.

Historical background

- 1965: Monoamine depletion
- 1978: Monoamine receptor upregulation
- 1982: The advent of SRIs

Monoamine depletion theory (1965)

- Independently (and almost simultaneously) formulated by two groups[1]
- The theory attempted to synthesize several earlier findings (that reserpine promotes depression, amitriptyline hinders peripheral 5HT uptake, iproniazid inhibits MAO, etc.)

1. Coppen A. The biochemistry of affective disorders. *Br J Psychiatry.* 1967;113(504):1237-1264.

Monoamine receptor upregulation theory (1978)

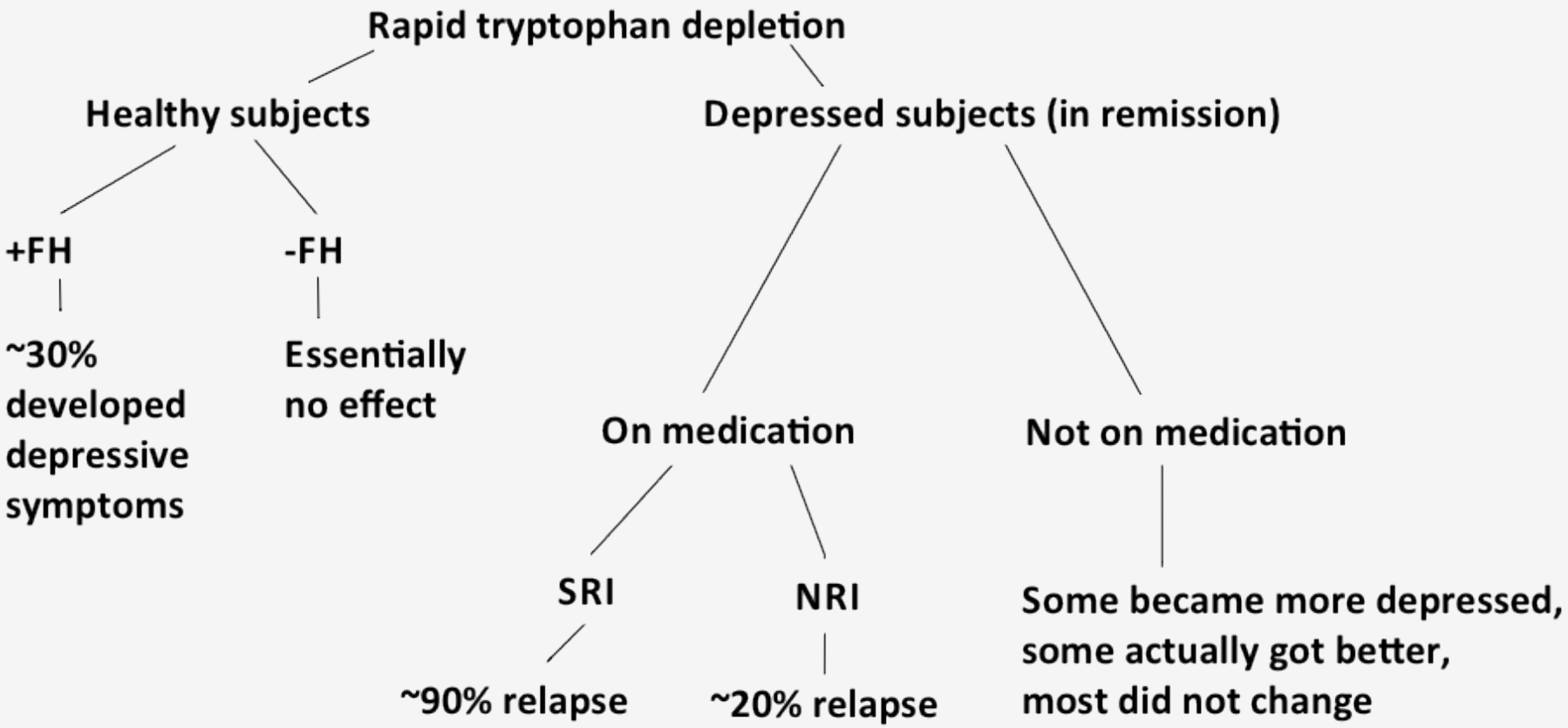
- An attempt to account for discrepancies between onset of pharmacological and clinical effect and the equivocal data regarding the effects of prolonged antidepressant treatment on monoamine levels)[1]

1. Sulser F, Vetulani J, and Mobley PL. Mode of action of antidepressant drugs. *Biochemical Pharmacology.* 1978;27 (3):257-61

The advent[1] of SRIs (1982)

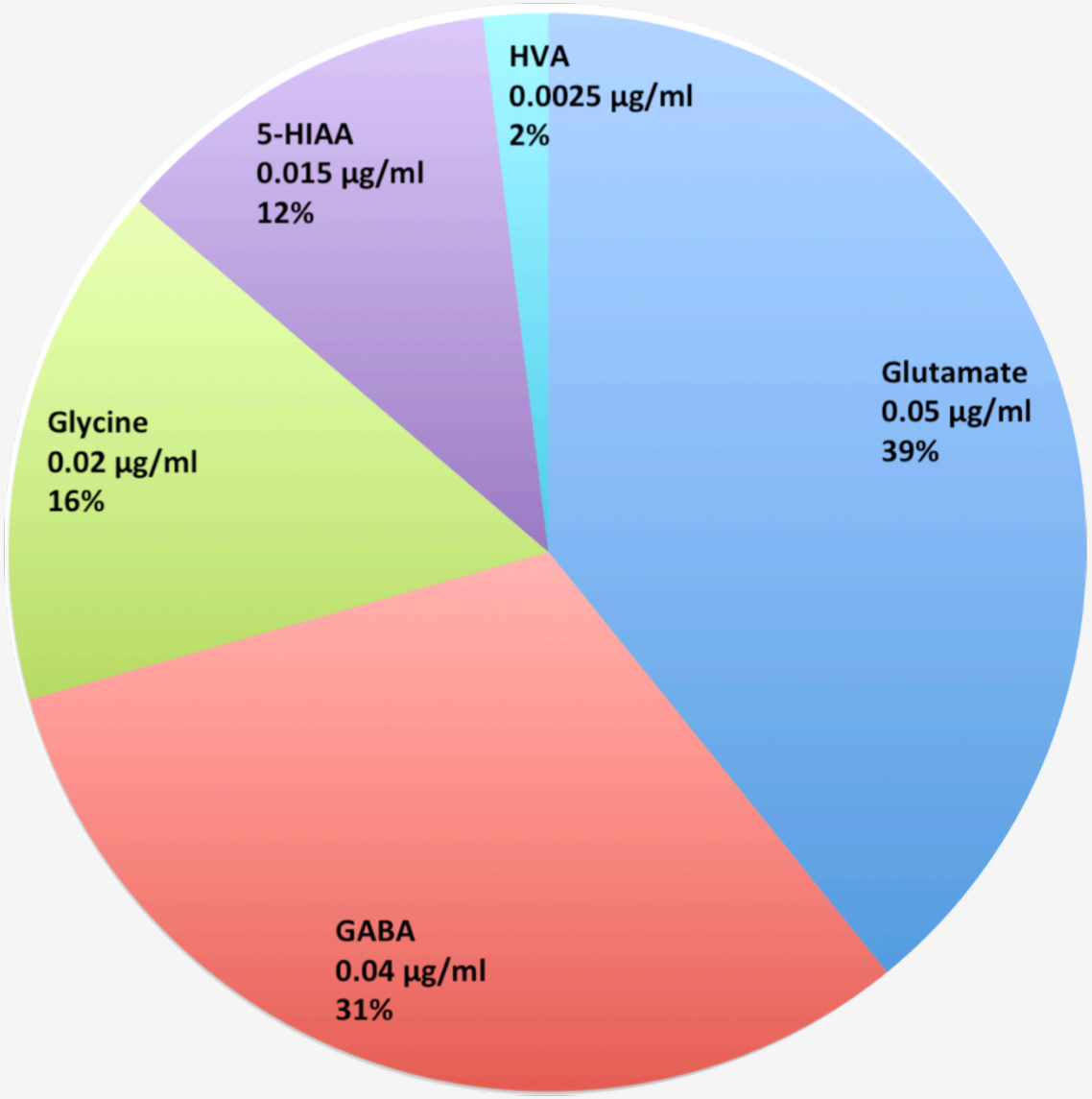
- It becomes convenient, though misleading, to refer to depression as a “low serotonin state”[2]

1. Georgotas A, Krakowski M, and Gershon S. Controlled trial of zimelidine, a 5-HT reuptake inhibitor, for treatment of depression. *Am J Psychiatry.* 1982;139:1057-58.
2. Blease C. The duty to be well-informed: the case of depression. *J Med Ethics.* 2013.



Rapid tryptophan depletion can cause medication responders to relapse, but does not consistently affect nonresponders[1]

1. Delgado PL. Depression: the case for a monoamine deficiency. *J Clin Psychiatry.* 2000;61[suppl 6]:7-11.



- **Relative extracellular concentrations of chemicals involved in neurotransmission**

- Values shown are averaged from microdialysis measurements made in the dorsal hippocampus of conscious male rats (n = 5)[1]

- Note that concentrations of glutamate and GABA obtained via microdialysis may in fact be substantially less than concentrations present at the synapse! [2]

1. Nencioni ALA, Barreto SA, Lebrun I, Florio JC, Lourenço GA, and Dorce VAC. Neurotransmitter evaluation in the hippocampus of rats after intracerebral injection of TsTX scorpion toxin. *J Venomous Animals and Toxins including Tropical Diseases.* 2009;15(2):236-254.
2. Westerink BH, and Timmerman W. Do neurotransmitters sampled by brain microdialysis reflect functional release? *Analytica Chimica Acta.* 1999;379(3):263-274.

Crosstalk between systems complicates depression's pathophysiology

- **Monoamine systems are not separate**
  - Agonism of 5HT receptors ($5HT_{2A}$, $5HT_{2C}$) indirectly downregulates DA and NE[1]
- **Brain circuits do not exist in isolation**
  - Disruption of one can provoke disruption of another
- **The complexity of derangements implies a similar complexity of clinical presentations**

1. Blier P, and El Mansari M. Serotonin and beyond: therapeutics for major depression. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536.

Changing definitions of depression: psychiatry's evolving nosology

- "Major depressive disorder" is a relatively modern concept
- Developed in the 1970s as part of a group of "Research Diagnostic Criteria" meant to improve reliability of psychiatric diagnosis

“There is no agreement within our field as to the generic name for an episode of serious depressive illness. We use the term 'major depressive disorder' as it seems general enough to encompass the many further subdivisions that are the basis of much current research. This category includes some cases that would be categorized as neurotic depression, and virtually all that would be classified as involutional depression, psychotic depression, and manic depressive illness, depressed type.”[1]

1. Spitzer RL, Endicott J, and Robins E. Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry.* 1978;35(6):773.

- In 1980 the RDC definition was incorporated into DSM-III
- It has remained essentially unchanged since

Inherent limitations of a unitary “major depressive disorder”

- Presentations are inevitably complex, yet because of the checklist approach, very different people with very different symptoms are lumped into the same category

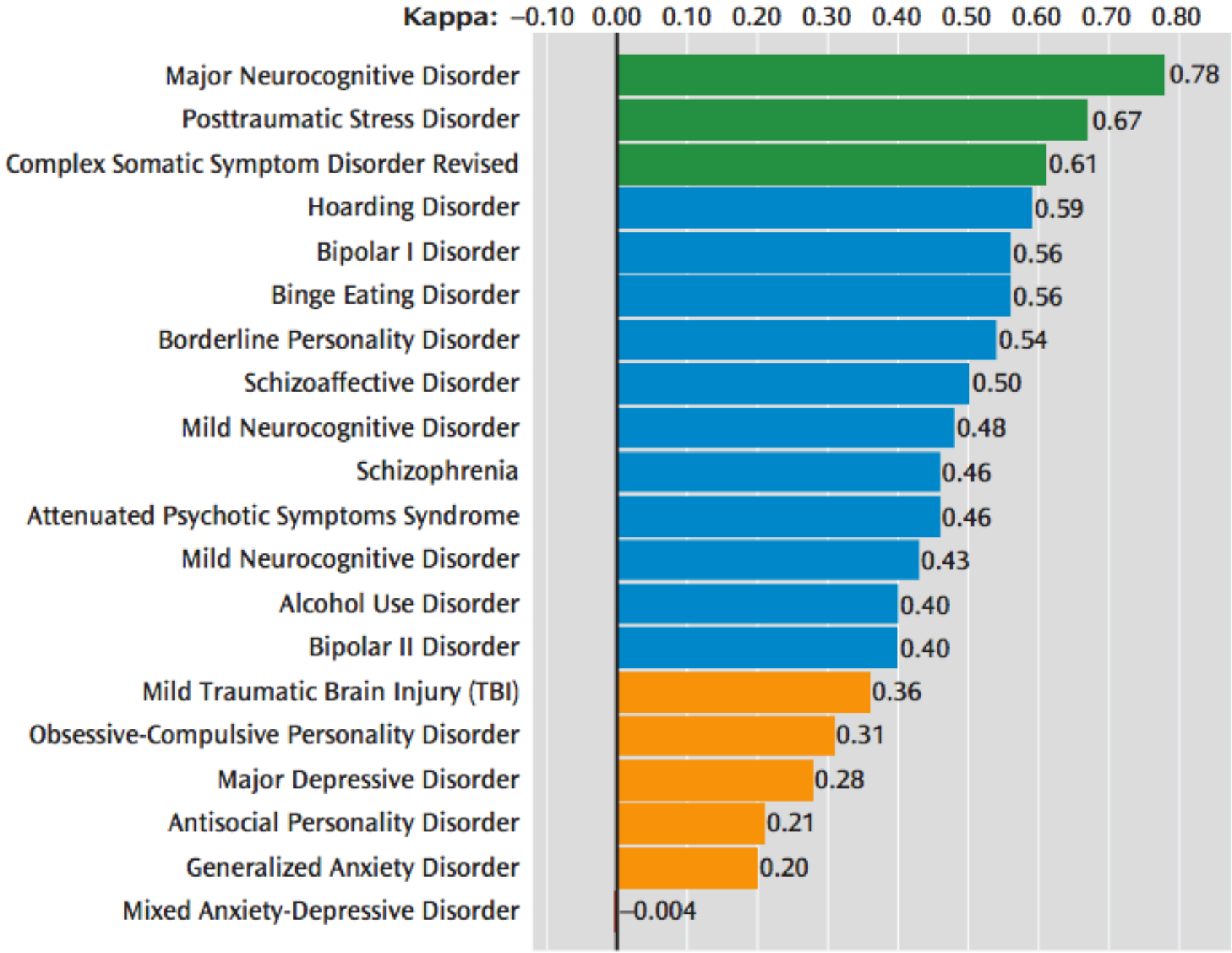
Inherent limitations of a unitary “major depressive disorder”

- **Melancholic** vs. **atypical** depression
- **Unipolar** vs. **bipolar** depression
- **Persistent** depression
- **Psychotic** depression
- Depression **with anxious distress**
  - **“Mixed anxiety-depressive disorder”**

κ in DSM-5 field trials

- Measurement of inter-rater reliability
- Quantifies the likelihood of nonrandom agreement between two clinicians regarding a diagnosis after a structured interview

- $\kappa = 1$ **perfect agreement**
- $\kappa = 0$ **agreement that would be expected by chance**



Freedman R, Lewis DA, Michels R, et al. The initial field trials of DSM-5: new blooms and old thorns. *Am J Psychiatry.* 2013;170(1):1-5.

RDoC: a circuit-driven approach[1] to mental illness, slicing depression along another axis

- **Negative valence**
  - Acute threat / Potential threat / Sustained threat / Loss / Frustrative nonreward
- **Positive valence**
  - Approach motivation / Initial responsiveness to reward / Sustained responsiveness to reward / Reward learning / Habit
- **Cognitive systems**
  - Attention / Perception /Working memory / Declarative memory / Language behavior / Cognitive (effortful) control
- **Systems for social processes**
  - Affiliation and attachment / Social communication / Perception and understanding of self / Perception and understanding of others
- **Arousal/modulatory systems**
  - Arousal / Biological rhythms / Sleep-wake

1. Cuthbert BN, and Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.* 2013;11:126.

Depression is heterogeneous

- Research is increasingly showing that “major depressive disorder” is a heterogeneous construct with complex determinants
- Monoamines alone may account for only a small fraction of this complexity
- Clinical symptoms, too, may be the tip of a much larger phenotypic iceberg

Biological correlates of depression

- Hyperconnectivity in the default mode network[1,2]
  - A collection of brain regions (vMPFC, PCC, MTL) that reliably deactivate during goal-directed behavior
- Hippocampal atrophy[3]

1. Posner P, Hellerstein H, Gat G, et al. Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry.* 2013:1-10.
2. Perrin P, Merz M, Bennett B, et al. Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. *PNAS.* 2012;109(14):5464-5468.
3. MacQueen G, and Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? *Mol Psychiatry.* 2011;16(3):252-64.

Biological correlates of depression

- Elevated cytokines[1]
- Exaggerated inflammatory response[2]
- Shortened telomeres[3]

1. Rosenblat JD, Cha DS, Mansur RB, and McIntyre RS. Inflamed moods: A review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry.* 2014.
2. Glaser R, Robles TF, Sheridan J, Malarkey WB, and Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Arch Gen Psychiatry.* 2003;60(10):1009.
3. Shalev I, Moffitt TE, Braithwaite AW, et al. Internalizing disorders and leukocyte telomere erosion: a prospective study of depression, generalized anxiety disorder and post-traumatic stress disorder. *Mol Psychiatry.* 2014.

Biological correlates of depression

- Strong association with physical symptoms[1]
  - WHO data: 25,916 patients in 14 countries were screened
    - 1,146 fit the definition of “major depression”
    - Of those, 69% initially had reported only physical symptoms as their reason for visiting the doctor

1. Simon GE, VonKorff M, Piccinelli M, Fullerton C, and Ormel J. An international study of the relation between somatic symptoms and depression. *New England Journal of Medicine.* 1999;341(18):1329-1335.

A new framework

- Two parallel theories:
  - **The “stress” hypothesis**
  - **The “sickness” hypothesis**

The “stress” hypothesis

- Depressed behaviors are a “low-risk strategy”[1,2] adopted in response to defeat
  - Stress causes neurobiological changes that will reduce the likelihood that the individual will engage in risk-taking behavior (thus minimizing his exposure to further harm or stress)

1. Price J, Sloman L, Gardner R, Gilbert P, and Rohde P. The social competition hypothesis of depression. *British Journal of Psychiatry.* 1994;164(3):309-315.
2. Gilbert P. Evolution and depression: issues and implications. *Psychological Medicine.* 2006;36(3):287-297.

The “stress” hypothesis

- Hippocampal volume loss is a robust finding in depression[1]
  - Increased stress leads to increased cortisol
  - Cortisol is neurotoxic to hippocampal cells
  - Hippocampal cell loss results in HPA axis disinhibition
  - Cortisol further increases
- Sparse dendritic spines in postmortem brains of depressed individuals
- Infusion of neurotrophins into rat brain promotes neural arborization and neuroplasticity[2]

1. MacQueen G, and Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? *Mol Psychiatry.* 2011;16(3):252-64.
2. Mamounas LA, Blue ME, Siuciak JA, and Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *The Journal of neuroscience.* 1995;15(12):7929-7939.

The “sickness” hypothesis

- “Sickness behavior” is an evolutionary response
- Historically, infection has been by far the leading cause of human death
- We evolved in this context

The “sickness” hypothesis

- Behavioral symptoms of depression may be a (once adaptive) means of conserving energy in the setting of debilitating illness and mitigating the damage that a contagious individual might wreak upon his social group
  - Withdrawal, apathy, anergia – all discourage the individual from infecting others
  - Suicide minimizes the chance that others will come in contact with him

The “sickness” hypothesis

- Increased cytokines and inflammatory markers found consistently in depression:
  - IL-1/2/6/8/12
  - IFN-gamma
  - TNF-alpha
- MS/HIV/IBD/RA all associated with depression
- Gut as major interface with the environment
  - Intestinal mucosal dysfunction and increased lipopolysaccharide[1]

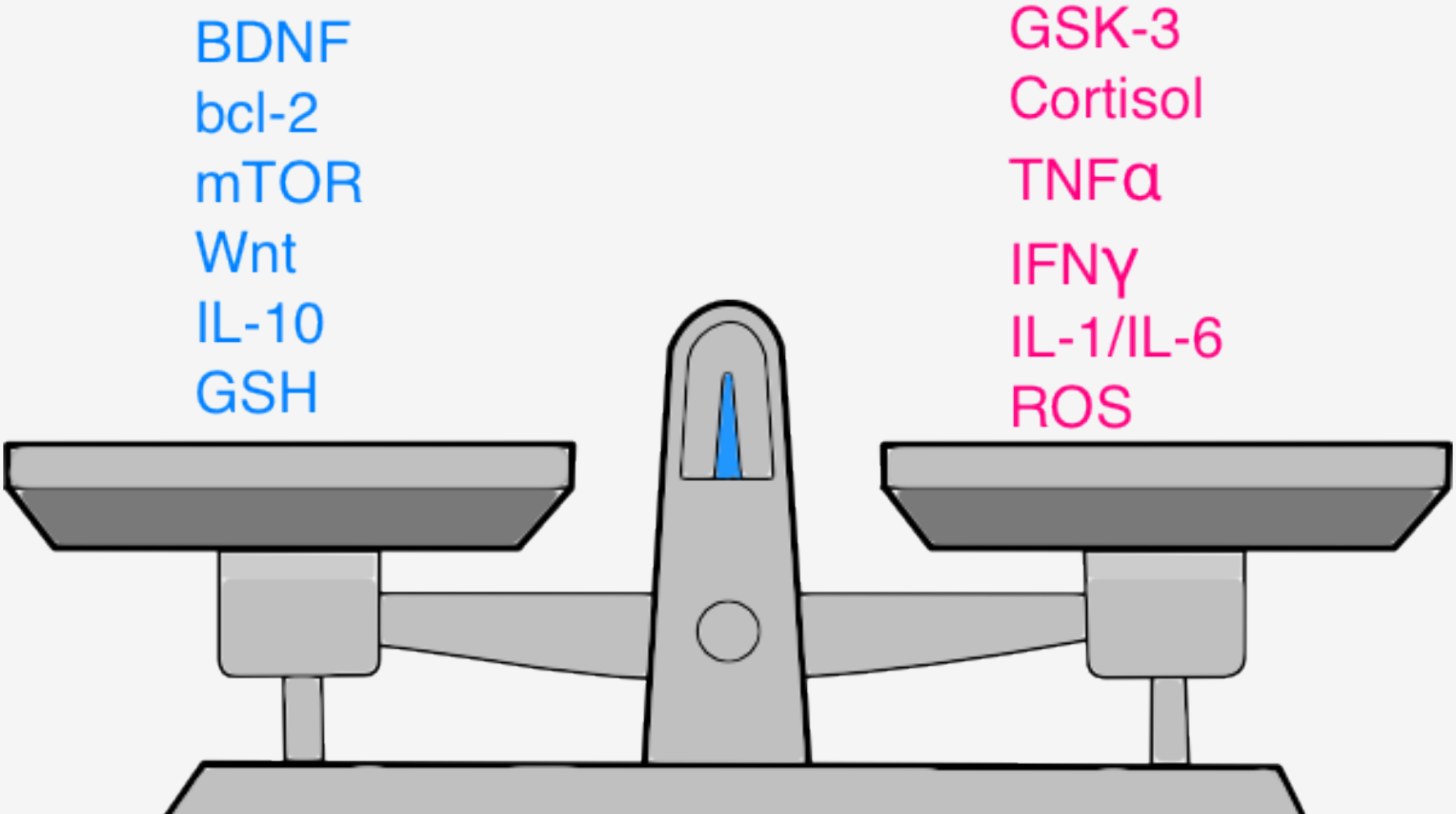
1. Maes M, Yirmyia R, Noraberg J, et al. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab Brain Dis.* 2009;24(1): 27-53.

“Stress” and “sickness” in context

- **Allostasis** maintains **homeostasis**[1]
- The brain interprets and responds to environmental challenges from moment-to-moment
- In the long term, this exacts a cumulative cost – **allostatic load,** which manifests as neuronal atrophy
- The extent of allostatic load is a function of genetic vulnerability and environmental factors
- In treating depression, it is important to be aware that homeostasis is precarious

1. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci.* 2004;1032:1-7.

There is a delicate balance between factors promoting **cell survival** and those promoting **cell death**



Novel treatments

infliximab

- 60 outpatients with depression, either on an antidepressant (n = 37) or not on medication (n = 23) were given an infusion of infliximab (n = 30) or placebo (n = 30) at 0, 2, and 6 weeks of a 12 week trial[1]
- There was no overall difference in response (measured via HAM-D) between the infliximab and placebo groups.
- However, when the data was analyzed, it was found that CRP levels (which had been drawn at baseline) predicted better response to infliximab than placebo

1. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry.* 2013;70(1):31-41.

curcumin

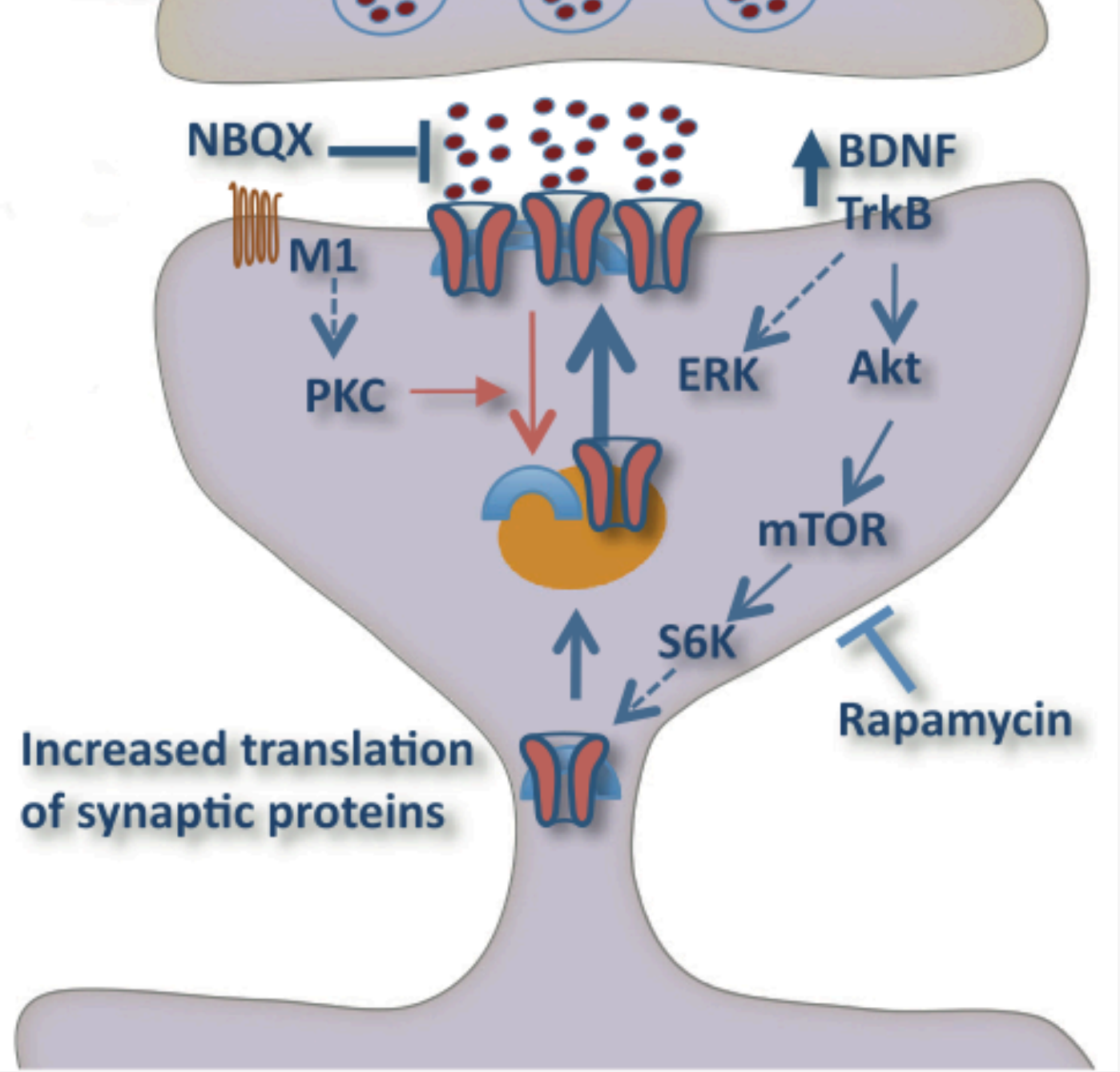
- Component of the spice turmeric
- **Inhibits TNFα** and increases BDNF expression
- 60 patients with depression randomized to fluoxetine (n = 20), curcumin (n = 20), or both (n = 20)[1]
- Tolerated well at 1g daily
- Equivalent numbers responded to fluoxetine (64.7%) and curcumin (62.5%)

1. Sanmukhani J, Satodia V, Trivedi J, et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytother Res.* 2013.

N-acetylcysteine

- Mitigates damage due to oxidative stress by replenishing glutathione
- Randomized, double-blind trial done in 2008[1]
  - n = 75; patients had bipolar disorder (maintenance phase)
  - NAC superior to placebo as adjunct to usual medication
  - Also well-tolerated at a dose of 1g bid

1. Berk M, Copolov DL, Dean O, et al. N-acetylcysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. *Biol Psychiatry.* 2008;64(6):468-75.



mTOR

Voleti B, Navarria A, Liu RJ, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry.* 2013;74(10):742-9.

ketamine

- Activates mTOR pathway
- Initial studies in 2000[1] and 2006[2] (n=7, n=17) were small but promising
- More recent 2012 study[3] was larger (n=24) and importantly included midazolam as active placebo
- Appears to compare favorably with ECT[4]

1. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* 2000;47:351-354.
2. Zarate CA, Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antag-onist in treatment-resistant major depression. *Arch Gen Psychiatry.* 2006;63: 856 – 864.
3. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* 2013;74(4):250-6.
4. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. *Psychiatry Res.* 2013.

ketamine

- Benefits: rapid response
- Drawbacks: response difficult to sustain (riluzole has been tried, unsuccessfully, as a relapse prevention strategy), concerns regarding neurotoxicity and psychotomimesis

scopolamine

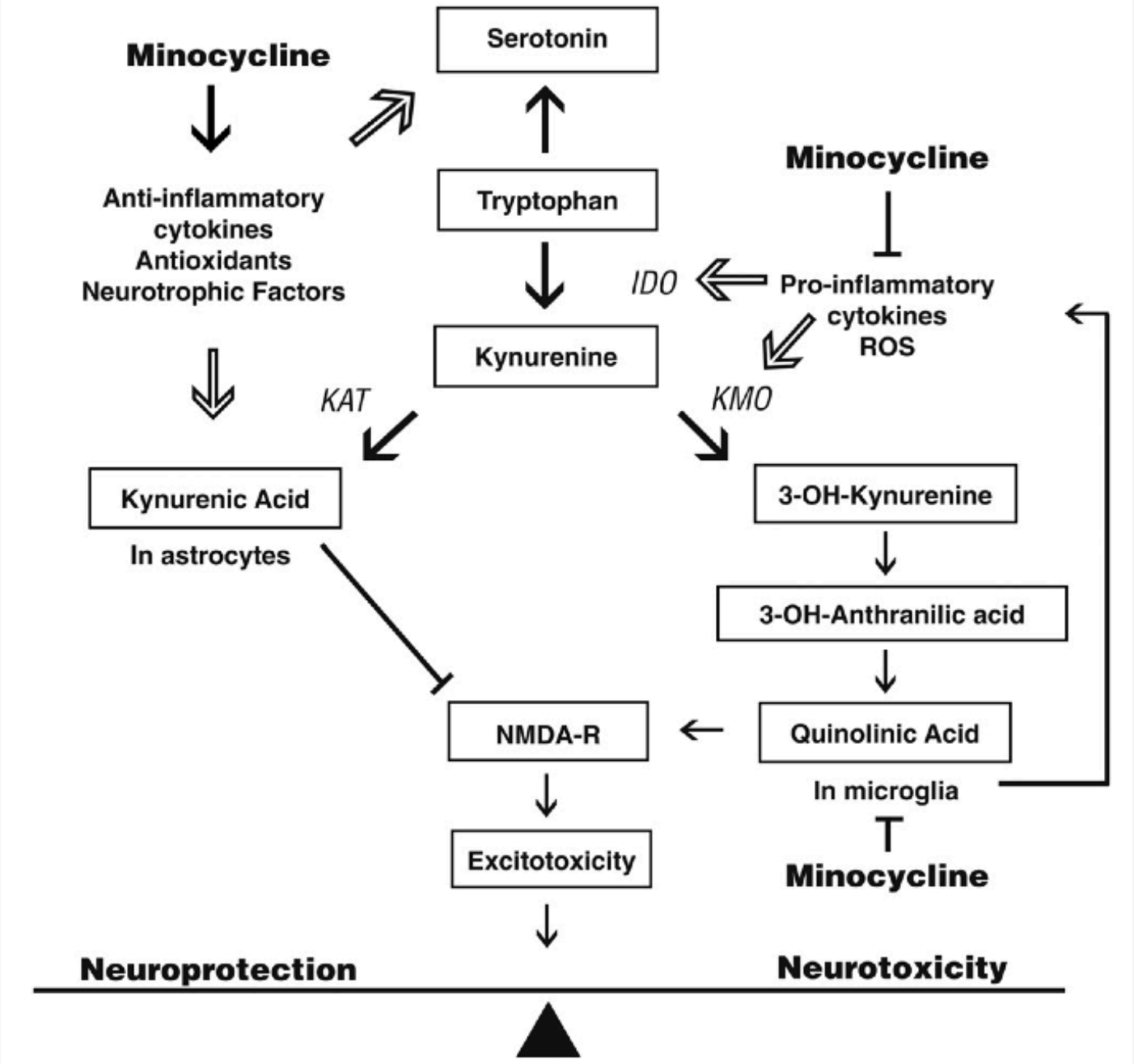
- Centrally-acting, competitive and nonselective mAchR inhibitor
- Mechanism of action
  - Original theory: depression may be characterized by an increase in Ach relative to NE/5HT/DA[1]
  - Recent data: likely works through mTOR[2]
- Half-life of 8 hours
- Effects 15 to 30 minutes after administration
- Penetrates brain more readily than other AchR antagonists

1. Janowsky DS, El-Yousef MK, and Davis JM. Acetylcholine and depression. *Psychosomatic Medicine.* 1974;36(3): 248-257.
2. Voleti B, Navarria A, Liu RJ, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry.* 2013;74(10):742-9.

minocycline

- Most lipid-soluble tetracycline antibiotic[1]
- Several animal trials, no human trials[2] (although has been studied for deficit symptoms in schizophrenia)

1. Soczynska JK, Mansur RB, Brietzke E, et al. Novel therapeutic targets in depression: minocycline as a candidate treatment. *Behav Brain Res.* 2012;235(2):302-17.
2. Savitz J, Preskorn S, Teague TK, Drevets D, Yates W, and Drevets W. Minocycline and aspirin in the treatment of bipolar depression: a protocol for a proof-of-concept, randomised, double-blind, placebo-controlled, 2x2 clinical trial. *BMJ Open.* 2012;2(1):e000643.



Soczynska JK, Mansur RB, Brietzke E, et al. Novel therapeutic targets in depression: minocycline as a candidate treatment. *Behav Brain Res.* 2012;235(2):302-17.

zinc

- Widespread effects: antioxidant effects, maintains immune function, regulates glutamatergic circuits (noncompetitively inhibits the NMDA receptor, preventing excitotoxicity)[1]
- Positive results with monotherapy[2]
- One small positive trial as antidepressant adjunct[3]

1. Swardfager W, Herrmann N, Mazereeuw G, Goldberger K, Harimoto T, and Lanctôt KL. Zinc in depression: a meta-analysis. *Biol Psychiatry.* 2013;74(12):872-8.
2. Sawada T, and Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. *Eur J Clin Nutr.* 2010;64(3):331-3.
3. Nowak G, Siwek M, Dudek D, Ziêba A, and Pilc A. Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. *Polish Journal of Pharmacology.* 2003;55(6):1143-1148.

anti-GSK-3 agents

- Directly inhibit cell death
- Perhaps the holy grail of antidepressants
- Agents that exist or are in development[1,2]:
  - **tideglusib** (in phase II trials for Alzheimer's)
  - **staurosporine** (bacterial isolate)
  - **Li, Be, Zn, Hg, Cu** (metal cations)

1. Kramer T, Schmidt B, and Lo Monte F. Small-molecule inhibitors of GSK-3: structural insights and their application to Alzheimer's disease models. *Int J Alzheimers Dis.* 2012;2012:381029.
2. Eldar-Finkelman H, and Martinez A. GSK-3 inhibitors: preclinical and clinical focus on CNS. *Front Mol Neurosci.* 2011;4:32

Summary

- Two large paradigm shifts now taking place
  - From the monoamine theories to a larger inflammation theory
  - From DSM to a more neurobiologically-driven diagnostic method
- Innovative treatments on the horizon

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- Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry.* 2013;70(1):31-41.
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