Rapid Treatments for Psychiatric Disorders

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Disclosures

- Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Definition of **rapid**?

- What did you think when you saw the title of this presentation?
- “Rapid” compared to SSRIs or antipsychotics?
- How do we compare with other specialties? (cardiology, anesthesia, neurology - stroke, pain, infectious disease)
- If you had acute pain from kidney stone and the only ‘effective’ treatment was a SSRI with a 45% response rate over 6 weeks how would you feel?
Vienna's Narrenturm—German for "fools' tower"—was one of the earliest buildings specifically designed for mentally ill people. It was built in 1784.
Rapid treatment of acute psychosis

• 24 patients with acute functional psychoses (schizophrenia or mania) were treated with intramuscular haloperidol in a three-hour period.

• 5mg -> +10 mg Q30min vs 5mg-> +5mgQhr

• There was almost complete remission of cardinal symptoms (thought disorder, hallucinations, and delusional activity) in this period for 11 patients. Acute dystonia, easily reversed, was the only significant side effect

Anderson WH, American Journal Psychiatry, 1976, 133 (9) 1076-1078
Rapid antidepressant psychotherapy?

Patient Change Trajectories **Over a Year** of Psychoanalytic Therapy and Psychoanalysis. Alex J. Behn Berliner, 2014, dissertation
I'm going to give my psychoanalyst one more year, then I'm going to Lourdes.

Woody Allen
Rapid for what problem?  
(Hint: Think emergency room setting)

- Violent behavior
- Psychosis
- Intoxication/Overdose
- Withdrawal
- Drug reaction or interaction
- Anxiety/Panic
- Depression /Suicidality
Rapid for what problem? - II

- Route of administration of drugs (IV/IM)
- Contain/restrain/stabilize
- Administer something that solve the problem (i.e. naloxone for opiate OD) or stabilize (IV benzodiazepine for alcohol withdrawal)
- We have “treatments” for conditions with known etiology
- Do we have treatments for conditions of unknown etiology?
Not talking about precision medicine! (Having fun with ICD-10?)

V97.33XD: Sucked into jet engine, subsequent encounter.

**Z99.89: Dependence on enabling machines and devices, not elsewhere classified. – PUT DOWN YOUR SMARTPHONES!**

W220.2XD: Walked into lamppost, subsequent encounter.

Y93D1: Stabbed while crocheting

Y23.1 Hunting rifle discharge, undetermined intent

Y93.D: Activities involved arts and handcrafts (you glued what?)

Z62.1 Parental overprotection (AKA helicopter parent, see your school district policies)

Z62.891 Sibling rivalry

Z73.1 Type A behavior pattern

R46.1: Bizarre personal appearance

Z73.4 Inadequate social skills, not elsewhere classified
How do we treat acute psychosis/agitation?

- Etiology not known
- Acute condition
- Old (cheap) drugs vs new expensive drugs
- What is better in terms of efficacy?
- Do we have “rapid” treatments? And how much would they cost?
Discharge instructions

Never drink like that again.
A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis.

- 172 patients, practical clinical trial, haloperidol (N = 56), risperidone (N = 61), and olanzapine (N = 55). Mean modal daily doses were 5.4 mg/day for haloperidol, 4 mg/day for risperidone, and 15.3 mg/day for olanzapine; 98.3% of subjects were drug naive at baseline.

- All 3 treatments showed similar effectiveness in reducing the severity of general, negative, and positive sx after 6 weeks. No statistical differences among groups.

- Extrapyramidal symptoms and concomitant anticholinergic medication use was greater with haloperidol than olanzapine or risperidone. Olanzapine-treated patients had significantly more weight gain vs haloperidol and risperidone groups.

Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation)

- 32 studies comparing haloperidol with 18 other treatments.
- Few studies reflect real world practice, most were small and carried considerable risk of bias.
- Haloperidol > placebo: asleep at two hours (2 RCTs, n = 220, risk ratio (RR) 0.88, 95% confidence interval (CI) 0.82 to 0.95). Dystonia was common (2 RCTs, n = 207, RR 7.49, CI 0.93 to 60.21).
- Three trials (n = 205) compared haloperidol vs lorazepam. There were no significant differences between the groups with regard to the number of participants asleep at one hour

Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses

- 4 trials **olanzapine IM vs. IM placebo** (total n=769, 217 placebo).
  - olanzapine IM > placebo at 2 hours (4 RCTs, n=769, RR 0.49 CI 0.42 to 0.59, NNT 4 CI 3 to 5) and olanzapine IM was as acceptable as placebo.
  - olanzapine IM did not seem associated with extrapyramidal effects
- 2 trials **olanzapine IM vs haloperidol IM** (total n=482, 166 allocated to haloperidol). No differences between olanzapine IM and haloperidol by 2 hours for the outcome of 'no important clinical response'
- 2 trials compared **olanzapine IM with lorazepam IM** (total n=355, 119 allocated to lorazepam). For the outcome of 'no important clinical response', there was no difference at 2 hours
- No studies reported outcomes related to hospital and service use, satisfaction with care or suicide, self-harm or harm to others.
- No studies evaluated the oro-dispersable form of olanzapine.

Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses

• “Data relevant to the effects of olanzapine IM are taken from some studies that may not be considered ethical in many places, all are funded by a company with a pecuniary interest in the result. These studies often poorly report outcomes that are difficult to interpret for routine care. Other important outcomes are not recorded at all.”

OUCH!

Let’s go back to the oldies then
Loxapine - Cochrane review (2007)

- 41 studies
- Compared with placebo, loxapine has an antipsychotic effect (Global effect - not improved at six weeks: n=78, 2 RCTs, RR 0.30 CI 0.1 to 0.6 NNT 3 CI 3 to 5).
- As effective as typical drugs in the short term (4 -12 weeks) (Global effect: n=580, 13 RCTs, RR 0.86 CI0.7 to 1.1; mental state: n=915, 6 RCTs, RR 0.89 CI 0.8 to 1.1).
- Very limited heterogeneous data suggest that, given intramuscularly (IM), loxapine may be at least as sedating as IM haloperidol and thiothixene (Navane).
- Loxapine is also as effective as atypicals (risperidone, quetiapine) (n=468, 6 RCTs, RR mental state not improved 1.07 CI 0.8 to 1.5).
- Adverse effect profile is similar to typicals - more extrapyramidal adverse effects when compared with atypicals (n=340, 4 RCTs, RR 2.18 CI 1.6 to 3.1).
Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine

Michael D. Lesem et al. BJP 2011;198:51-58

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Loxapine - Results and limitations

- Loxapine is FDA approved for the acute treatment of agitation associated with schizophrenia or bipolar disorder in adults
- 18 sites to recruit 129 patients over a year and half (7.2pts/site)
- Pts needed to be able to read and provide informed consent, to understand and follow technique for device
- Bronchospasm is a black box warning and that there is a Risk Evaluation and Mitigation Strategy (REMS) to assess prior to prescribing and monitoring the patient after each administered dose.
Loxapine - Results and limitations - II

• The people who need this medication are generally medically complex, may have street drugs in their system, are generally cigarette smokers and their pulmonary and in many cases their cardiac status may be unknown. If the initial dose is not effective, the question becomes - now what?

• It can only be given in a registered health care facility by personnel who can assess and manage any pulmonary complications.

• **60 capsules** of loxapine 10mg (generic) 32.84 $

• average wholesale price for **ONE 10-mg package of Adasuve**  $145 -> often not on formulary
Uh-oh..
Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside 
A Randomized, Double-blind, Placebo-Controlled Trial

• Single low-dose sodium nitroprusside IV (0.5 μg/kg/min for 4 hours) to 20 patients with schizophrenia taking antipsychotics

• Outcome: changes in positive, negative, anxiety, and depressive symptoms during the following 4 weeks.

• (0.5 to 10 μg/kg/min dose rates for hypertension)

• Mechanism? modulate the NMDA–nitric oxide–cGMP pathway

From: Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside: A Randomized, Double-blind, Placebo-Controlled Trial


![Figure Legend:]

Mean Total 18-Item Brief Psychiatric Rating Scale Scores. A, Scores during the first 12 hours; B, scores at 4 weeks. Asterisks indicate statistically significant P values as given in the text; error bars, SEMs.
ICD-10 Quiz: Can You Spot the Y92 Code That Isn’t Real?

- Y92.000 – Kitchen of unspecified non-institutional (private) residence as the place of occurrence of the external cause
- Y92.026 – Swimming pool of mobile home as the place of occurrence of the external cause
- Y92.156 – Swimming pool of reform school
- Y92.232 – Corridor of hospital
- Y92.254 – Theater (live)
- Y92.311 – Squash court
- Y92.415 – Exit ramp or entrance ramp of street or
- Y92.61 – Building (any) under
- Y92.65 – Oil rig as the place of occurrence of the external cause
- Y92.72 – Chicken coop as the place of occurrence of the external cause
- Y92.74 – Orchard as the place of occurrence of the external cause
- Y92.78 – Vineyard as the place of occurrence of the external cause
- Y92.820 – Desert as the place of occurrence of the external cause
- Y92.86 – Slaughterhouse as the place of occurrence of the external cause
Let’s shift gear...
Let’s talk about ECT

- Meta-analysis, the overall remission rate was 50.9% (n = 402/790) for patients with MDD and 53.2% (n = 168/316) for patients with BP dep. (Dierckx B. Bipolar Disord. 2012)

- 73 patients with BP-TRD. RCT ECT (3x wk, RUL, brief) vs algorithm-based pharmacological treatment.

- **Response** significantly higher in the ECT group (73.9% versus 35.0%), but the **remission** rate did not differ between the groups (34.8% versus 30.0%).

How fast is the response to ECT?

• Depressed patients often begin to respond after the first treatment and progress to wellness with 6 to 12 treatments.

• There is **considerable variability** in the trajectories, somatic symptoms usually improve first.

• Patients who respond early in a course of ECT have a greater likelihood of ultimately achieving remission.

How fast is the response to ECT? II

• In a study carried out by the Consortium for Research in ECT (CORE) 34% of 253 patients achieved remission (HAM-D score of 10) at or before the 6th session with ECT (within 2 weeks) and 65% achieved remission at or before the 10th session (within 3 to 4 weeks).

• 54% had an initial first response (decrease of 50% in HAM-D score) by session 3.

• Furthermore, 19% of the seriously ill cohort in this study (baseline HAM-D score of approximately 35) experienced remission with 4 or fewer ECT sessions.

How fast is the response to ECT? III

• Balancing speed of response to ECT in major depression and adverse cognitive effects
• Speed of response was significantly greater with ECT x 3/wk but this schedule induced more severe memory impairment, even when the number of ECT in the series was not significantly different between the two groups.

Other neurostimulation techniques
Cranial Electric Stimulation

  - 120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD
  - Six-week treatment of 2-mA anodal left/cathodal right prefrontal tDCS and sertraline (50 mg/d)
- Barclay and Barclay. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. Affect Disord. 2014
  - N= 115, primary diagnosis of an anxiety disorder
  - all intakes were performed at the principal investigator’s private practice location.
A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients.

- 2-site, randomized, active sham-controlled (1:1)
- 9 sessions of rTMS over 3 days as adjunctive to usual inpatient for suicidality treatment. The setting was two inpatient military hospital wards (one VA, the other DOD).
- screened approximately 377 inpatients, yielding 41 adults. Comorbid PTSD, TBI or both
- SSI scores declined rapidly over the 3 days for both groups (sham change -15.3 points, active change -15.4 points), with a trend for more rapid decline on the first day with active rTMS (sham change -6.4 points, active -10.7 points, P = 0.12).

Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression.

- Six-week double-blind sham-controlled treatment trial of a novel device - low-field magnetic stimulation synchronized to an individual's alpha frequency
- 202 subjects comprised the intent-to-treat (ITT) sample, and 120 subjects completed treatment per-protocol (PP).
- There was no difference in efficacy between active and sham in the ITT sample.

Low field magnetic stimulation

- Serendipitously discovered during an MRI study of bipolar depressed patients using echo-planar magnetic spectroscopic imaging (EP-MRSI) (similar to, but different from the pulse sequences used in FMRI).

- The electric fields generated by the EP-MRSI scan were smaller (0.7 V/m) than fields used in repetitive transcranial magnetic stimulation (rTMS) treatment of depression (1-500 V/m) and also extended uniformly throughout the head, unlike the highly nonuniform fields used in rTMS.
Low field magnetic stimulation

Portable electromagnetic device that reproduces only the rapidly oscillating (1 kHz, <1 V/m) electromagnetic field of the experimental procedure.
Low field magnetic stimulation

- Antidepressant-like effects of LFMS on immobility in the forced swim test (FST) (Carlezon Biol Psy 2005)
- Randomized, double-blind, sham-controlled in medicated, depressed patients with either BPD (n = 41) or MDD (n = 22).Received a single 20’ treatment (Rohan, Biol Psy 2013)
- Improvement (>10%) in mood was observed following LFMS treatment relative to sham treatment for primary outcomes, the VAS and the HDRS-17 in the combined sample (p = .01 VAS, p = .02 HDRS-17)
- Large study at DCRP and other sites as double-blind sham controlled through the UO1 RAPID network (LFMS as augmentation of antidepressant for MDD, failed one AD)
Guess what is going to be the next topic..
How about medications for depression? ("Rapid" in 1991)

A Preliminary, Open Study of the Combination of Fluoxetine and Desipramine for Rapid Treatment of Major Depression

- 14 inpatients, responses were retrospectively compared with those of 52 inpatients treated with desipramine alone
- One week after treatment began, the mean change in Hamilton Depression Rating Scale scores was 42% in the group that received Fl+D and 20% in the group that received D alone (Mann-Whitney U Test, $P = .007$).
- At 2 weeks, the mean change in scores of the group that received Fl+D was 60%, while a 30% change was noted in the patients treated with D alone ($P = .001$).
- 10/14 patients remitted

How about medications for depression? (2015)

Augmentation with

• Aripiprazole
• Quetiapine
• Stimulants/modafinil
• Pramipexole
• Lamotrigine
• Minocycline
Decreased resting-state connectivity between neurocognitive networks in treatment-resistant depression, de Kwaasteniet et al., Front. Psychiatry, 2015
SSRI cause rapid changes
Serotonergic Modulation of Intrinsic Functional Connectivity

Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmaco-fMRI: A randomized cross-over study

• A single dose of selective serotonin reuptake inhibitor to spark a widespread connectivity decrease throughout the brain
• Localized increases in connectivity from cerebellar and thalamic regions in addition to a connectivity decrease in most cortical and subcortical areas
• Supports a conceptual framework of serotonergically modulated functional connectivity in long-range circuits.

Antidepressant response to aripiprazole augmentation associated with enhanced FDOPA utilization in striatum: a preliminary PET study

• (PET) with the DOPA decarboxylase substrate 6-[18F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA), which has been used extensively for imaging of the presynaptic dopaminergic system in brain.

• Fourteen depressed patients, who had failed 8 weeks of antidepressant therapy with selective serotonin reuptake inhibitors, underwent FDOPA PET scans before and after aripiprazole augmentation; eleven responded to augmentation.

• Increased FDOPA trapping in the right medial caudate of augmentation responders

A randomized controlled trial of the efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with residual symptoms of MDD after treatment with escitalopram

- After 8 weeks of open-label escitalopram, randomized to 6 weeks of lisdexamfetamine dimesylate (20-50 mg/d) or placebo augm.
- 129 pts
- Lisdexamfetamine dimesylate augmentation reduced depressive symptoms in participants with inadequate escitalopram response.

Open-Label Study of Minocycline (150 mg/day) as Adjunctive Therapy for Patients with Unipolar Psychotic Depression (n=25)

Fig. 1. HAM-D total score at each assessment from baseline to week 6 (ITT, LOCF).

How about lamotrigine augmentation in MDD?

Double-Blind Study of Lamotrigine (up to 400 mg/day) Augmentation of Paroxetine in TRD Patients (n=96)

Barbee et al, J Clin Psychiatry 2011; 72(10):1405-1412
ICD-10
OMG codes

a set of codes dedicated solely to healthcare practitioners and the symptoms and signs they have developed secondary to introduction of ICD-10.

OMG 000.01 – ICD-10-induced chest pain, noncardiac
OMG 000.03 – ICD-10-induced hypertensive emergency
OMG 000.10 – #$%@ giant migraine due to ICD-10, need Advil
OMG 000.16 – #$%@ giant migraine due to ICD-10, need to quit medicine
OMG 000.20 – Nervous breakdown due to ICD-10, sucking thumb, left
OMG 000.24 – Insomnia due to ICD-10, unable to cry self to sleep
OMG 000.29 – Injury to dominant hand from hitting computer screen due to ICD-10, straight punch
OMG 000.39 – Seizure secondary to unspecified ICD-10 nonsense, generalized tonic-clonic
OMG 000.43 – Unable to distinguish ICD-10 code from USPS tracking number
MDD with psychotic features: the story of Mifepristone

- Dysregulation of the hypothalamic-pituitary-adrenal axis has been postulated in the pathophysiology of psychotic depression.
- Mifepristone is a potent and specific antagonist of glucocorticoid receptor (GR-II) and the progesterone receptor. Little effect on the mineralocorticoid receptors, no known affinity to monoamine, histamine, or cholinergic receptors.
- The GR-II receptor has a low affinity for cortisol and appears to play a part in the termination of the stress response.
- Mifepristone does not appear to be associated with suppression of glucocorticosteroid actions peripherally.
Yes, that Mifepristone

• **Mifepristone** (or **RU-486**) is a synthetic, steroidal antiprogestogen and antiglucocorticoid

• method of first-trimester abortion, a 600-mg dose

• 10mg doses as an emergency contraceptive
Mifepristone – early clinical trial

- 29 sites in USA
- BPRS score of 38 or greater and HAM-D-24 score of 20 or greater
- Double-blind, placebo-controlled, parallel group design. Patients received mifepristone 600mg/day or placebo for seven consecutive days.
- Antipsychotics and antidepressants were not allowed for at least 7 days prior to randomization and for the 7 days of study drug administration.
- Endpoint = percentage of patients who had Rapid Response (at least a 30% reduction in the BPRS Total) at days 7 and 28.

Mifepristone – early clinical trial

- Efficacy analyses on the Intent to Treat (ITT) sample (n = 221), or all randomized subjects who received at least one dose of study medication.

- **Mifepristone > placebo** for response on the primary measure, a 30% **improvement in the total BPRS** (Rapid and Sustained Response and Response). This difference was statistically significant in the ITT sample (p = .041) and completer samples (p = .020).
Mifepristone – late clinical trials

• 29 sites, N=258 patients
• Breslow–Day test indicated a statistically significant site-by-treatment interaction. Mifepristone produced significantly higher response among the twenty sites who participated from the trial onset ($p < .05$), whereas no difference was observed at the nine sites added late in the trial.
• Between 2006 and 2007, 2 phase III trials failed to meet their endpoints.
Increase sample size to gain statistical power does not necessarily increase power...

Adding patients that are not from the targeted population or adding sites with inadequate experience in conducting standardized protocols can threaten internal validity of any RCT

Christine M. Blasey, Charles DeBattista, Robert Roe, Thaddeus Block, Joseph K. Belanoff

*A multisite trial of mifepristone for the treatment of psychotic depression: A site-by-treatment interaction*

Contemporary Clinical Trials, Volume 30, Issue 4, 2009, 284–288
Where to find the results of trial?

**Impact Factor**

- **Positive result**: Biol Psychiat
- **Negative result**: Contemp Clin Trials
Anti-glucocorticoids in Mood Disorders

- Safety and effectiveness of anti-glucocorticoid agents in the treatment of mood episodes (manic, mixed affective or depressive) with placebo or other drugs
- 9 studies met criteria for inclusion, including mifepristone, ketoconazole, metyrapone and DHEA. Three trials were in patients with psychotic major depression (pMDD), 5 trials in non-psychotic major depression and 1 trial in bipolar disorder.
- No significant difference overall for response to anti-glucocorticoid treatment over placebo, although the mean change in HAM-D scores indicated a significant difference in favor of treatment (WMD -4.54, 95 % CI: -6.78 to -2.29).
- Of the 5 trials in non-psychotic depression (unipolar or bipolar), there was a significant difference favoring treatment (HAM-D 50 % reduction: RR 0.72, 95 % CI: 0.56 to 0.91).
- In pMDD, there was no evidence of an overall anti-depressant effect (HAM-D 50 % reduction: RR 0.98, 95 % CI: 0.79 to 1.22) or an effect on overall psychopathology (BPRS 30 % reduction: RR 0.96, 95 % CI: 0.76 to 1.22).
- Considerable methodological differences exist between studies

I'M NOT MAD
JUST DISAPPOINTED.
Scopolamine

• Centrally acting competitive inhibitor of the muscarinic cholinergic receptor.
• Minimal effects on nicotinic receptors.
• Selectivity for muscarinic receptors, high potency for all five muscarinic receptor subtypes, slow dissociation rate from central muscarinic cholinergic receptors, and rapidly entering brain.
• Currently used for post-operative nausea, GI disorders, motion sickness.
• Among the TCAs, AMT has the highest potency for muscarinic receptors, affinity for muscarinic receptors that is similar in magnitude to its affinity for monoamine transporters. At therapeutic doses of AMT, most of the serotonin transporter sites are occupied, as well as a large proportion of muscarinic sites.
• *Furey and Drevets (Arch Gen Psych 2006)* double-blind, randomized, placebo-controlled crossover, 18 depressed patients: 9 with MDD and 9 with BD. 3 infusions of scopolamine 4.0 µg/kg (3–5 days apart). All patients demonstrated at least a partial response, and 10 patients experienced remission. No patients experienced mania.

• Dose-finding study on 8 MDD patients, random, double-blind, 15-minute IV infusion of saline placebo or scopolamine: 2.0, 3.0, and 4.0 µg/kg. The mean change in MADRS score between baseline and session 4 was $-13.8\pm7.7$ ($p<.002$). Five subjects showed a >50% reduction in the MADRS score, and three remitted (MADRS < 10).
Scopolamine III

• *Drevets and Furey (Biol Psych 2010)*, another double-blind, randomized, placebo-controlled crossover study, 22 MDD. The scopolamine- group had a 32% reduction in MADRS scores, compared with a 6.5% reduction in the placebo group. The effect persisted for 12 to 16 days after the final scopolamine infusion. Eleven patients experienced remission.

• *Furey et al Neuropsychoph 2010*, added 12 subjects. Greater AD effect in women

• *Khajavi 2012*, 40 pts with MDD oral scopolamine (1mg) as augmentation of citalopram, higher response rate (65 % vs 30%) at wk 6
Scopolamine - IV

- AEs: Blurred vision, dry mouth, light-headedness, transient (2-4 hours)
- No subject developed delirium, psychosis, overt confusion, clinically significant cardiovascular effects, or treatment-emergent suicidal ideation
- No subject developed hypomania.
- Relief from depressive symptoms on the first morning after scopolamine infusion
Antidepressant Efficacy of Scopolamine (4 mcg/Kg)

Furey and Drevets, Arch Gen Psychiatry. 2006;63:1121-1129
Scopolamine mechanisms?

- NMDAR gene expression is enhanced by muscarinic receptor stimulation in at least some brain structures.
- Li et al (Science 2010) reported that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling protein expression and increased number and function of new spine synapses in the rodent prefrontal cortex.
- Blockade of mTOR signaling interrupted ketamine induction of synaptogenesis and the associated antidepressant-like, behavioral responses in rodent models.
- The same group demonstrated that scopolamine also induces the mTOR pathway at a timing and magnitude similar to ketamine (Neuroscience Meeting presentation 2011).
Ketamine - Clinical efficacy

• A single low dose of ketamine IV improved depressive symptoms within 72 hours (n=7 patients with treatment-resistant depression -TRD) (Berman, Biol. Psychiatry, 2000).

• Zarate et al. 2006: double-blind, placebo-controlled, crossover study: single ketamine infusion had fast and sustained antidepressant effects in 17 patients with TRD (Arch General Psychiatry).
  – 71% of subjects were improved 24 hrs after infusion.

  -Replicated in other samples in patients with MDD and BP depression
Ketamine Mechanism(s) of action: preclinical studies

- Rats exposed to chronic unpredictable mild stress (three weeks) developed anhedonia-equivalent and decreased synaptic spine density in the prefrontal cortex.
- Single ketamine injection of 10 mg/kg (IP): reversal of anhedonia-like behavior, regain of body weight (Li et al. Science, 2010).
- Elevated levels of synaptic proteins, synaptic density, and postsynaptic current (EPSC) responses—rapid enhancement of the structure and function of cortical synapses by ketamine.
- Effects sustained for 7 days.
- Blockade of mammalian target of rapamycin (mTOR) pathway prevented these effects.
- Ketamine-induced synaptogenesis and antidepressant behavior. (Li et al. Science 2010).
Ketamine Mechanism(s) of action

Increase glutamate transmission, increase synaptogenesis

Adapted from Duman et al., Science, 2012
Ketamine Mechanism(s) of action - II

- Neurobiological mechanisms of ketamine’s antidepressant actions are more complex than NMDA receptor blockade.
- Primary mechanism of action is blockage of the NMDA receptor at the PCP site within the ionotrophic channel.
- -> disinhibition of GABAergic inputs and enhancing the firing rate of glutamatergic neurons, increases the presynaptic release of Glu
- This increase in Glu release then preferentially favors AMPA receptors over NMDA receptors because the latter are blocked by ketamine
- The net effect of ketamine on a cellular level is an increased glutamatergic throughput of AMPA relative to NMDA
- Increased glutamatergic activity (Maeng et al. Biol. Psychiatry, 2008)
Ketamine imaging studies


- Functional MRI study: ketamine decreased activity in ventromedial PFC, orbital cortex, and SGACC, with increased activity in posterior cingulate and other cortical regions (Deakin et al. Arch. Gen Psych., 2008).

- All neuroimaging studies done in healthy populations.
Ketamine Safety and tolerability

• Moderate anxiety, irritability, headache, increased libido.
• Analgesia, anesthesia, brief hyper- or hypotensive episodes, tachycardia or bradycardia, bradypnea (aan het Rot et al. Biol. Psychiatry, 2010).
• Most adverse effects peaked within 40 minutes and ceased within 80 minutes post-infusion (Zarate et al., 2006).
• 205 intravenous (IV) ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants with DSM-IV-defined major depressive disorder (MDD) pooled from 3 clinical trials
• Overall antidepressant response rate, (≥ 50% improvement in MADRS), was 67%.
• 4 of 205 infusions (1.95%) were discontinued due to AEs. The overall attrition rate was 3.1%.
• In the first 4 hours after the infusion, the most common general AEs were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Approximately one third of individuals experienced protocol-defined hemodynamic changes.
• No cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

Ketamine vs. Placebo in Unipolar and Bipolar Depression

Major depression

Bipolar depression

Dotted Line = Placebo
Solid Line = Ketamine

‡P< 0.001; †P < 0.01; and *P < 0.05.


Courtesy Dr Ionescu
Ketamine vs. Midazolam in TRD

Murrough et al, Amer J Psych. 2013

p≤0.02;

Courtesy Dr Ionescu
Ketamine vs. Midazolam in TRD

- Ketamine (N=47)
- Midazolam (N=25)

Response Rate (%)

- Day 1: Ketamine 60%, Midazolam 25%
- Day 2: Ketamine 60%, Midazolam 20%
- Day 3: Ketamine 50%, Midazolam 20%
- Day 7: Ketamine 40%, Midazolam 20%

Courtesy Dr. Ionescu

Murrough et al, Amer J Psych 2013
Ketamine and suicide

- Price et al: patients with TR MDD have reduced MADRS suicide subscale scores 24 hrs after a single ketamine infusion (n=26, Biological Psychiatry, 2009).

- DiazGranados et al: 33 patients with TRD received a single ketamine infusion: suicidal ideation scores decreased at 40 minutes, remained significantly decreased for 4 hours (Journal of Clinical Psychiatry, 2010).

- Larkin et al. reported similar findings in an emergency room setting in patients with depression and SI. Patients received single ketamine bolus, with changes in MADRS scores at 40 minutes that persisted 10 days. (n=14, open-label, Int. Journal of Neuropsychoph 2011).
Ketamine studies at MGH

- Ketamine as ADD-on to treatment-as-usual
- OPEN –LABEL
- 14 depressed patients very treatment-resistant with suicidal ideation
- 6 infusions of ketamine over 3 weeks.
- Escalating dose if no response
- 5 patients out of 12 completers (41.7%) were responders, and 2 out of 12 were in remission (16.7%).
- 5/12 had no suicidal ideation
- Response lasted approximately 2-3 weeks
Repeated-Dose Ketamine for Suicidal Ideation

CSSRS-Ideation Score

Baseline (n=14) Infusion 1 (n=14) Infusion 2 (n=14) Infusion 3 (n=13) Infusion 4 (n=13) Infusion 5 (n=12) Infusion 6 (n=12)

Time

p<0.001

Ionescu et al, J Clin Psych 2015
Ongoing areas of research

• Identification of other compounds targeting the glutamate system that could have similar efficacy, better tolerability, and less abuse potential.
  – AZD6765 or lanicemine (Sanacora, 2013. 3 infusions per week, TRD) – AZ dropped its development
  – GLYX 13 (Burgdorf 2013) Naurex obtained ‘Fast Track’ from FDA, as add-on

• Development of therapeutic strategies (augmentation) to increase ketamine efficacy and duration of action.

• Dose-finding study (RAPID network)

• Dissecting ketamine’s mechanism(s) of action and neurobiological correlates.
Bridging clinic and research

• At MGH we opened the first ‘ketamine clinic’ for TRD associated with academic center
• Patients involved in research, in their own monitoring (“stakeholders”), in identifying augmentations and interactions of concomitant drugs
Any questions?
Some ICD-10 codes still under consideration for ICD-11

- 000.01 – Accident in, on, around or within a bouncy castle, red, initial encounter
- 000.04 – Killed softly by his song, The Fugees’ cover version
- 000.07 – Tickled to death during pajama party, Tuesday night, intentional
- 000.14 – Accident in, on, around house while rooting for favorite sports team not during playoff run
- 000.25 – Injury to self-esteem upon encounter with family member, maternal unit, over breakfast
- 000.28 – Abdominal injury sustained while laughing out loud (LOL), joke was a pun
- 000.30 – Left buttock injury from misaimed dart, bar, first encounter
- 000.34 – Exsanguination due to paper cut, left pinky finger
- 000.35 – Food poisoning from hot dog picked up from off the curb, major city (not Manhattan)
- 000.42 – Fractured face from irresponsible use of a hammock
Massachusetts General Hospital
Department of Psychiatry

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