

A MIND THAT FOUND ITSELF

BY

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Introduction

Clifford Beers – 1908, mental hygiene movement

The necessity of early intervention – Kindling

1. Theology

- a. Galatians 6:2
- b. Psalms 34:4
- c. Psalms 56:3

2. Psychology

- a. Support
- b. Problem Solving
- c. Pandora's Box - Caution
- d. Hope and Ego Glue

3. Physiology

a. Kindling

Kindling is a term perhaps used more in neurology concerning seizures, but it has ramifications to psychiatry. I would define kindling as a phenomenon by which a psychiatric condition becomes more resistant to treatment the longer it is left untreated. Kindling also has implications that every episode of some mental disorders does brain damage. The further implication is that significant mental disorders should be treated early.

1. In bipolar disorder:

- 1 episode – 50% chance of another
- 2 episodes – 70% chance of another
- prodromal symptoms are similar to MDD but less intense and include: ↑ energy, ↑ anger, ↑ thoughts, ↓ sleep, ↓ judgment, ↑ sexuality, mood swings

2. In depression of old age:

- 1 episode – 40% chance of another
- 3 episodes – 80% chance of another

- prodromal symptoms include: ↓ mood, anhedonia, ↓ appetite, ↓ sleep, ↑ anger, ↑ guilt, ↓ thinking, death thoughts, self-harm
3. In schizophrenia treatment of prodromal symptoms might ↓ disability. Prodromal symptoms similar to the symptoms of schizophrenia but less intense and include:
- social withdrawal, asocial
 - ↓ motivation, amotivation
 - ↓ emotional expression, flat affect
 - avolition
 - ↓ thoughts
 - ↓ attention, ↓ focus
 - ↑ suspiciousness
 - odd thought content
 - odd behavior
 - bizarre thinking
 - sad mood

Neuroimaging techniques sometimes document the anatomical damage of the above disorders.

- Bipolars sometimes have atrophy in the amygdala; schizophrenics have less brain volume; depressives have atrophy in frontal cortex and hippocampal; alcoholics can have neuronal loss. These damages might be truncated with early treatment.

b. Bipolar Disorder

1. Current treatment strategies

Current treatment strategies for bipolar disorder include:

- atypical antipsychotics: Olanzapine plus fluoxetine (Symbyax) and quetiapine (Seroquel) are approved for bipolar depression; only quetiapine is approved for bipolar II depression. The atypicals are effective in bipolar mania and some have antidepressant effects.
- mood stabilizers: Lamotrigine (Lamictal) is a little better than even lithium in depression. Divalproex

(Depakote) and carbamazepine (Tegretol) are effective manic mood stabilizers; gabapentin (Neurontin), topiramate (Topamax), and tigabine (Gabril) are good for adding in comorbid conditions; the jury is still out on zonisamide (Zonegran) and levetiracetam (Kappra). Lamictal is approved for maintenance treatment of bipolar disorder, but not for acute episodes. Tigabine is being tried; it should be started low (seizure risk if induction is too rapid).

- lithium: Lithium is better in a manic episode but helps some in mood.
- typical antipsychotics: The typical antipsychotics such as Haldol are effective in mania but may add to depression.
- antidepressants: The antidepressants have been used in bipolar disorder; they may lift mood but can induce mania.
- drug combinations: Three quarters of patients in clinical practice may need more than one drug.
- other adjunctive drugs tried for various aspects of bipolar disorder include: pramipexole (Mirapex), provigil (Modavilil), asenapine (neuroleptic with less weight gain), and fish oil (omega 3 fatty acids).
- Dilantin: Dilantin might help in bipolar disorder, but it often has troublesome side effects.
- Other drugs have been used for comorbid disorders such as substance disorder (60%), anxiety disorder (60%), and borderline personality disorder (30%).

c. TCA's

Adding a TCA to a MAOI can precipitate serotonin syndrome (CNS, CV, GI, musculoskeletal symptoms); however, a MAOI has, at times, been added to a TCA. Both a MAOI and a TCA have, at times, been started together at low doses. Thus,

- great caution when adding TCA to MAOI (this can be deadly)
- caution with MAOI to TCA (amitriptyline or trimipramine)

- caution with MAOI to TCA at same time
- consideration of a 2 week (5 weeks with Prozac) wait when changing from SSRI/TCA to MAOI
- consideration of a 4 week wait when changing from MAOI to SSRI. Remember some of the MAOIs bind irreversibly. Ensam wait is often 1 to 2 weeks before starting another antidepressant.

d. MAOIs compared

- first MAOI: iproniazid (Marsilid), 1957
- most sexual dysfunction: phenelzine (Nardil)
- least sexual dysfunction: selegiline (Ensam)
- most side effects overall: phenelzine (Nardil)
- least side effects overall: selegiline (Ensam)
- most sedating: phenelzine (Nardil)
- least sedating: selegiline (Ensam), tranylcypromine (Parnate)
- most weight gain: phenelzine (Nardil)
- least weight gain: selegiline (Ensam), tranylcypromine (Parnate)
- most likely to cause insomnia: tranylcypromine (Parnate)
- least likely to cause insomnia: selegiline (Ensam)
- most likely to cause ↓ BP: phenelzine (Nardil)
- least likely to cause ↓ BP: selegiline (Ensam)
- most likely to cause stimulation: tranylcypromine (Parnate)
- least likely to cause stimulation: phenelzine (Nardil), isocarboxide (Marplan)
- least likely to cause a hypertensive crisis: selegiline (Ensam)

e. Selective serotonin reuptake inhibitors (SSRI)

SSRI's are used for many disorders in psychiatry—major depressive disorder (MDD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), panic disorder, premenstrual dysphoric disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), and eating disorders. They have been used off-label for premature ejaculation and autism. They include Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Luvox (fluvoxamine), Celexa (citalopram), and Lexapro (escitalopram).

f. Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)

Cymbalta (duloxetine), Effexor (venlafaxine), and sibutramine (Miridia) are SNRIs. Effexor is approved for major depressive disorder (MDD), generalized anxiety disorder (GAD), and social anxiety disorder. Cymbalta is approved for MDD, GAD, and diabetic neuropathic pain; it has also been used for stress urinary incontinence. By modulating ascending and descending pain fibers Cymbalta decreases pain. Miridia (sibutramine) is approved for weight loss. Abrupt discontinuation of Effexor has at times produced a discontinuation syndrome (aches, chills, fatigue, dizziness, and sleep disturbance). Effexor has also increased blood pressure in some people. They work as antidepressants by blocking the reuptake of both serotonin and norepinephrine as the dose is increased. Effexor also has some blocking of dopamine as the dose is increased even higher. Pristiq (desvenlafaxine) is a new SNRI.

- g. Serotonin-dopamine antagonists (SDA's—atypical neuroleptics)
The SDA's were originally approved for schizophrenia; later most were approved for bipolar disorder. They include Risperdal (risperidone), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), and Invega (paliperidone). The original SDA was Clozaril (clozapine) in 1989. Invega (paliperidone) which is a metabolite of risperidone was approved for schizophrenia in 2007. Their mechanism of action seems nothing short of brilliant:
- On the postreceptor side they block D2 and by doing this in the limbic brain hallucinations and delusions abate.
 - On the postreceptor side they also block 5HT2A and 5HT2C which increase dopamine in the frontal lobes so the negative symptoms of schizophrenia (flat affect, alogia, amotivation, asocial) tend to decrease. By contrast, the old neuroleptics that decreased dopamine in the frontal lobes tended to increase the negative symptoms of schizophrenia.
 - On the postreceptor side the blockage of 5HT2A and 5HT2C results in increased dopamine in the basal ganglia so that extrapyramidal symptoms are often less than with the old neuroleptics.

- More dopamine is released in the tuberoinfundibular pathway and therefore, prolactin does not increase.
- Thus, dopamine decreases in the limbic system but increases in the frontal lobes, basal ganglia, and tuberoinfundibular pathway. In other words, dopamine blockade wins over dopamine release in the nigrostriatal pathway so the positive symptoms of schizophrenia decrease, but dopamine release wins over dopamine blockade in the mesocortical pathway (so ↓ negative symptoms of schizophrenia), in the nigrostriatal pathway (so ↓ EPS), and in the tuberoinfundibular pathway (so ↓ prolactin).
- It seems that at least some of these may have antidepressant effects. For example, Seroquel mildly blocks a 5HT_{1D} autoreceptor on the presynaptic side which indirectly increases serotonin which should have an antidepressant effect; it also increases 5HT_{1A} on the presynaptic side (antidepressant effect); in fact, it has approval for bipolar disorder-depression. It also blocks a norepinephrine transporter which produces an antidepressant effect. Also, Geodon on the presynaptic side blocks the reuptake of serotonin, norepinephrine, and dopamine, which should have antidepressant effects; it also has a 5HT_{1A} agonist effect on the presynaptic side which conceivably produces an antidepressant effect. It also is an autoantagonist at 5HT_{1D} which should increase serotonin which could have an antidepressant effect. All of the SDA's block 5HT_{2A} and 5HT_{2C} receptors on the presynaptic side which should increase dopamine which should have antidepressant effects.

Abilify (aripiprazole) is also an atypical neuroleptic but its mechanism of action is different. It is a partial D₂ agonist. Partial D₂ agonists compete at D₂ receptor sites with dopamine and thereby lower dopamine which is high in schizophrenia. In essence it raises dopamine in the mesocortical pathway (in the frontal lobes) so the negative symptoms of schizophrenia decrease; it increases dopamine in the nigrostriatal pathway (in the basal ganglia) producing less extrapyramidal symptoms; it lowers dopamine in

mesolimbic pathway (in the limbic brain) decreasing the positive symptoms of schizophrenia; it inhibits 5HT_{2A} receptors in the tuberoinfundibular system so prolactin release is not stimulated (in traditional antipsychotics D₂ is blocked in the tuberoinfundibular pathway and since dopamine inhibits prolactin release, prolactin increases). In other words, there is an antagonistic and reciprocal relationship between serotonin and dopamine in the release of prolactin. In essence, one has more dopamine in the tuberoinfundibular pathway so prolactin does not increase as much as it does with traditional antipsychotic. However, Risperdal may not follow this rule, and prolactin may rise more often with it than other atypical neuroleptics which might limit its use more in some teenage females. Abilify has more FDA approvals for various aspects of bipolar disorder and schizophrenia than any other atypical neuroleptic. Zyprexa and Seroquel cause the most weight gain of the atypical neuroleptics. Geodon may cause the least. Clozapine is the most dangerous increasing the risk of agranulocytosis and seizures.

Conclusion