AVOIDING SERT INHIBITION

Selective serotonin reuptake inhibitors (SSRIs) include Prozac (fluoxetine), Paxil (paroxetine), Celexa (citalopram), Lexapro (excitalopram), Zoloft (sertraline), and Luvox (fluvoxamine).

Selective serotonin norepinephrine reuptake inhibitors (SNRIs) include Effexor (venlafaxine) and its metabolite Pristiq (desvenlafaxine), Cymbalta (duloxetine), Fetzima (levomilnacipran) and Savella (milnacipran) – and both Vybriid (vilazodone) and Trintellix (vortioxetine) contain this mechanism.

These medicines can work very well for depression, various forms of anxiety, irritability, and more – but they have attendant problems, and I don't like to burden clients with additional medicines to treat one or more of them. I also am concerned re complications of discontinuation.

As Fetzima has very little SERT inhibition, and Trintellix is a modulator of six neurotransmitters (not including) serotonin, with poor receptor occupancy at SERT even at the maximum dose, I do use them, but I use the others in rare situations when other options have been exhausted.

ADVERSE DRUG REACTIONS

- Sexual SEs are present in 40–70% of clients
  - In 1990's statistic was 2%; people were less forthcoming, and this was before use of the ASEX instrument in assessment
  - *Side effects may be enduring/persistent https://is.gd/ex8GAK, and https://rxisk.org/post-ssri-sexual-dysfunction-pssd/*
- Weight gain: especially w/ Paxil but possible with any SSRI; this is both hypothalamic (hunger) and due to an effect on stretch receptors in the stomach; clients don't know that they're full
  - Over time, SSRIs cause lack of glycemic control.
- Sleep disturbance: compression of REM sleep and less sleep efficiency (time asleep divided by time in bed); sleep can feel "fussy", less deep sleep (N3, delta, slow wave sleep), can cause periodic movements of sleep or restless legs syndrome as there is a shunting of dopamine towards serotonin. Some clients sleep as much as 12 or more hours per day because their sleep is not restful.
- Poor energy, late afternoon slump: in addition to having disturbed sleep, energy may be less because of a downtune in norepinephrine and dopamine, two "exciting" neurotransmitters. Clients get a siesta in the late afternoon. This is not less in SNRIs.
- Changes in affect, feeling dulled/"masked", or dragging; attenuated amplitude and range of emotion/numbness, and/or anhedonia (lack of pleasure).
- Cognition: drive/motivation, concentration, and other aspects of executive function and clarity may decrease (due to effects on dopamine and norepinephrine, and also histamine and acetylcholine, all involved in cognition) – these medicines are some of the worst for people living with signs/symptoms of ADHD and related disorders. We have uncovered function and brightness by tapering them, particularly Paxil.
- Movement disorders including akathisia, which with agitation is responsible for some of the suicidality that arrises from SSRIs. Sertraline has more effect on dopamine than other SSRIs, and thus more incidence of akathisia.
- Psychiatric side effects: "roughening" or quickening of mood, for people on the bipolar spectrum. Those with cyclic mood states [even if they have never experienced (hypo)mania] may experience a "mixed" or rough quality to their depressions, with agitation, irritability, racing/crowded thoughts, and more. There may be a quickening, with episodes coming closer together and more spontaneously, when SSRIs or particularly SNRIs are added. Some people also spike to (hypo)mania, and mixed states may include suicidality.
  - In meta-analyses mood switch occurs only in 15% of subjects, but it is not possible to measure subtle roughening or increase in cyclicity, which is very common. We see more rapid cycling with mixed states nowadays than we used to (say, in the 1990s) prior to widespread use of SSRI/SNRIs by primary care, after cursory evaluations.
  - Sertraline is the worst culprit here – I have personally seen more psychiatric side effects with this medicine than with other SSRIs. Historian David Healy found a letter in the "file drawer" at Pfizer admitting this medicine causes more psychiatric ADRs than others in class. https://davidhealy.org/?p=585

OPPOSITIONAL TOLERANCE and its distinction from Withdrawal, Rebound, and Recurrence

- Withdrawal syndromes are easily recognizable, and don't last long (unless an SNRI is being tapered over months)
- Rebound symptoms can be distinguished from relapse (into the same episode) or recurrence (of a new episode) as they are a bit more dramatic (for most unipolar depressed individuals, depression creeps in; with rebound symptoms they hit hard and quickly) – involving sleep disturbance, anxiety, dysphoria, irritability, cognitive issues.
- Genuine relapse or recurrence (variably defined by how far out from remission the person is) tends to look like the depression preceding it.
- Oppositional tolerance (pharmacodynamics mechanism) –
  - Mood is improved with the antidepressant, and the brain pulls in the opposite direction, to balance – as described by a colleague studying the phenomenon
  - When the drug is removed, in some people the brain doesn't snap back into its previous tone
  - Giovanni Fava describes this tolerance as "drug treatment may recruit processes that oppose the initial acute effects of the drug", referencing for the concept Young and Goudie, 1995, and hypothalamic pituitary adrenal (HPA) axis derangement is implicated; ketoconazole may treat, and antipsychotics also flatten the cortisol curve.
  - This "post-acute withdrawal" is a risk where serotonin is involved, can involve any drug affecting this system in particular ways (see G Fava 2011 and other papers for mechanisms), and we see it most commonly in SSRIs and SNRIs, perhaps due to the wide use of these agents.
  - Every person I've met who has experienced this syndrome has said it's worse than other depressions, with prominent dysphoria, irritability, usually with suicidality, and with autonomic dysregulation (of cardiovascular system, gastrointestinal, etc., as seen in hypercortisolemia). One person said her "nerves glowed blue." Another thought it was somewhat violent menopause, with constant crying and panic (all symptoms but climacteric). This feels a lot like rebound symptoms, only quite pronounced, and with the autonomic nervous system involvement.
  - In many people, restarting the medicine that is being or has been tapered fixes the issue. Dramatically, in jst a few days – which is confirmatory.
    In others it does not.
    - A colleague's a client discontinued Cymbalta on her own after 5 yrs on it, and over the past 3 years she has been trialed on numerous other agents and has also tried transcranial magnetic stimulation (TMA) and electroconvulsive therapy (ECT), she has had multiple hospitalizations, nothing has worked. Some suffer with post-acute withdrawal as many as 9 or 10 years without resolution.
    - Another colleague and I have had 50 people gathered from the website www.urvivingantidepressants.org that we have considered interviewing for a paper on this topic. All developed the tolerance to SSRIs or SNRIs.
    - Giovanni Fava has written papers on it, which I can offer on request.

SSRIs and SNRIs can be serviceable, depending on your expectations, though I've long been frustrated by their side effects and the need to use other medicines to address those, and after recognizing oppositional tolerance in my clients and watching them desperately and painfully endure it, while seeing others develop a more cyclic and rougher course of depressive illness, I learned to avoid using these medicines going forward.