Case 1

A 29-year-old right handed man with a history of epilepsy, depression, anxiety, ADHD, and alcohol use disorder is concerned about his psychiatric medications in terms of seizure risk. He has had 2 generalized tonic clonic seizures in the past month. He takes 450mg bupropion, 100mg quetiapine, 15mg Dexedrine, 100mg sertraline. He is also on 250mg BID lamotrigine for idiopathic generalized epilepsy. Prior medication trials included levetiracetam and zonisamide, neither of which he tolerated due to worsening depression. He also endorses drinking 5-6 beers daily.

Questions

1. Which of his psychiatric medications most elevates his seizure risk?

   Bupropion

2. Are psychostimulants such as Dexedrine safe for patients with epilepsy?
   Yes. ADHD is commonly comorbid with epilepsy, and there is data in children and adolescents supporting the safety of psychostimulants including amphetamines in patients with epilepsy. That said, abuse of stimulants including supratherapeutic doses or using methamphetamine on the street can cause seizures. It is possible some patients may experience a worsening of seizures with therapeutic doses of methylphenidate or amphetamines but it is not the rule.

3. Can patients with epilepsy take bupropion? Under which circumstances?
   Bupropion reliably causes seizures in overdose and has a dose-dependent increased seizure risk. This is most evident for the immediate release formulation at doses of 600mg of greater. According to the FDA "During the initial development, 25 among approximately 2,400 patients treated with WELLBUTRIN experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below for an incidence of 0.33% (3/1,000) within the recommended dose range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence)." They note a seizure incidence of 0.4% in patients at 450mg with the immediate release formulation.

   The SR and XL formulations appear to carry a lower risk of seizures. Doses of 300mg or less are mostly likely safe. 450mg is now the maximum licensed dose given the seizure risk above this. Patients with other risk factors including alcohol abuse, may not be good candidates for bupropion. Patients with otherwise well controlled epilepsy who do not tolerate or respond to other medications could be considered for bupropion. If the epilepsy is not relatively well controlled, it may be best avoided. The antidepressants with the highest seizure risk are clomipramine (still used for refractory OCD) and amoxapine (almost never used). These medications should generally be avoided in patients with epilepsy.

4. Which anti-seizure medicines likely confer the highest risk of worsening his psychiatric symptoms?
   Levtiracetam, zonisamide, topiramate, and brivaracetam are most likely to worsen psychiatric symptoms and caution should be given to using these medications in patients with pre-existing psychopathology. Depression, irritability, aggression, suicidal ideation, and rarely frank psychosis can occur. There was a time in the early 2000s when topiramate was used as a mood stabilizer and for that reason, it is sometimes erroneously used in patients with mood disorders. However, there is no good evidence supporting this and contradictory dating showing adverse effects on mood and cognition. As such, it should not be used in the treatment of mood disorders and used with caution in patients with such a history.

Table 18.1 Summary of the known behavioural profiles of antiepileptic drugs

AEDs	Positive effects			Negative effects		
	Antidepressant	Mood stabilizing	Anxiolythic	Depression	Irritability aggressiveness	Psychosis
Phenobarbital, primidone			+	+	+	
Phenytoin		+				+
Ethosuximide					+	+
Carbamazepine, oxcarbazepine		+				
Valproate		+	+			
Clonazepam, clobazam			+	+	+	
Vigabatrin				+	+	+
Lamotrigine	+	+			+	
Gabapentin			+		+	
Topiramate				+	+	+
Tiagabine				+	+	
Levetiracetam				+	+	+
Pregabalin			+	+		
Zonisamide				+	+	+

+ = Effect present.

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Case 2

A 40 year old right handed man with history of autism spectrum disorder, depression, relapsing remitting MS, and temporal lobe epilepsy reports worsening depression including suicidal thoughts. His current medications include 100mg topiramate XR and natalizumab 300mg q4

weeks. His epilepsy is well controlled. His most recent MRI brain and spine shows no evidence of active demyelination or new lesions, and redemonstrating multiple T2 FLAIR hyperintensities periventricularly as well as multiple cerebellar white matter lesions and mild FLAIR hyperintensity of the left hippocampus. He reports a remote history of taking sertraline and escitalopram. Both were helpful for his depression but he experienced sexual dysfunction and emotional numbing which was intolerable and thus discontinued. He would like to take another antidepressant, but not one that would cause sexual dysfunction.

Questions

1. What risks factors for depression does this patient have?
   Autism spectrum disorder, prior history of depression, MS, temporal lobe epilepsy, exposure to topiramate and possibly natalizumab (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853678/). One study suggested this medication can improve mood in patients with MS (e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4426783/) but there are also case reports of possible depression and suicidality. While epilepsy is a risk factor for depression, particularly if a temporal or frontal lobe focus, because it is well controlled it is less likely to be a contributor.

2. What kind of sexual dysfunction can occur with SSRIs?
   Low libido, anorgasmia, erectile dysfunction, delayed ejaculation, and persistent genital arousal have all been described with SSRIs.

3. What is the purported mechanism of SSRI-induced apathy/emotional blunting?
   Theories including stimulation of 5-HT2a receptors affecting dopamine release in prefrontal cortex

4. What potential antidepressant options could be considered in this patient?
   Mirtazapine, bupropion and vortioxetine are newer antidepressant options that do not typically cause sexual dysfunction (though vortioxetine probably most likely out of these to affect sexual functioning). Some patients who cannot tolerate SSRIs may tolerate the older TCAs. Despiramine is the best tolerated of the TCAs as it is less anticholinergic and antihistaminergic than other TCAs. It can still cause sexual dysfunction but less often than SSRIs. Because this pt's epilepsy is well controlled, it could be reasonable to consider bupropion XL formulation at the lower end of the dose range.

Case 3

A 45 year old right handed woman with a history of migraine, fibromyalgia, chronic pelvic pain is seen for evaluation of episodic weakness. She also reported some depressed mood and anxiety. During her examination, she had involuntary muscle spasms. These were characterized by hip thrusting and opisthotonos-like posturing. Prior evaluation included MRI of the brain, lumbar spine, EMG/NCS including repetitive stimulation, lab testing (including pseudocholinesterase,

AChR antibodies, anti-SSA/SSB antibodies, ANA, dsDNA, CK, aldolase, MuSK antibodies, anti-VGCC Abs), EEG, and muscle biopsy all of which disclosed no abnormalities. Prior medication trials included gabapentin, Lyrica, venlafaxine and duloxetine for pain symptoms, none of which she was able to tolerate.

Questions

1. The patient is diagnosed with a functional neurological disorder with mixed symptoms. What psychotropic medications are indicated for the treatment of this condition?

   Medications are not typically effective of FND and should be avoided for FND symptoms per se. The exception may be PPPD (persistent post postural dizziness) where there is some minimal data for use of antidepressants including SSRIs. Medications may be used for comorbid mood or anxiety disorders, or for pain or fatigue. Occasionally psychostimulants may be used in patients with persistent post-concussive syndrome or functional cognitive disorder.

   In general PRN medications for functional symptoms (e.g. benzodiazepines, hydroxyzine) should be avoided as they may worsen course overall by preventing fear extinction, reinforcing catastrophic/harmful beliefs about symptoms, and undermining patient's own resources. We want to empower patients to confront unpleasant emotions rather than dull them.

2. What medications may be helpful for her pain symptoms? What would you want to be mindful of?

   She has not tolerated SNRIs or gabapentinoids. I often find patients with somatoform disorders can tolerate TCAs such as nortriptyline or amitriptyline well, even if they don't tolerate the newer antidepressants. Patients with functional somatic syndromes, with comorbid mood disorder or symptoms such as tension type headaches, migraines, or central sensitization pain may benefit from a trial of one of these medications. Because patients with a somatic idiom of distress often develop adverse effects with medications it is important to start low and go slow. TCAs can also be used for comorbid depression and anxiety. The dose for psychiatric symptoms needs to be higher than pain symptoms alone (e.g. target of at least 75mg nortriptyline or 100mg amitriptyline), typically starting at 10mg qhs and increasingly in weekly 10mg increments as tolerated.

Case 4

A 72 year old left-handed man with idiopathic Parkinson's disease that was diagnosed 5 years ago develops visual hallucinations and paranoia. He reports seeing bugs, believes intruders are breaking into his home, and sees water leaking from the ceiling which is not noted by his wife or son. His treatment includes carbidopa/levodopa, entacapone, rasagiline, pramipexole and melatonin. His wife administers his medications and reports he is taking his medications as expected.

1. What neuropsychiatric syndromes commonly occur in patients with Parkinson's Disease?

   Depression, anxiety, apathy/athymhormia, psychosis, dopamine dysregulation syndrome, impulse control disorders (e.g. pathological gambling, hypersexual behaviors, kleptomania), and punding behaviors (i.e. repetitive complex motor behaviors) not uncommonly occur in PD.

2. Which medications commonly worsen or precipitate psychosis in Parkinson's Disease?

   Anticholinergics, MAO-B inhibitors (selegiline, rasagiline), COMT inhibitors (entacapone), dopamine agonists (pramipexole, ropinirole), and levodopa can contribute to Psychosis in Parkinson's Disease.

3. What kinds of visual hallucinations are most commonly reported in Parkinson's disease psychosis?

   Passage hallucinations (e.g. animal passing by someone's side) and presence hallucinations (sensing another person next to or behind them) are the most common VHs in PD. Illusions also commonly occur. Less specific, fully formed complex visual hallucinations can also occur. Auditory hallucinations are much less common in PDP. Severity of cognitive symptoms, duration of PD symptoms, and daytime somnolence seem to correlate with Parkinson's disease psychosis.

4. What medications are most helpful for the management of Psychosis in PD? When would you use them?

   If the psychosis is non-distressing or non-impairing it does not need treatment at all. If it is, we first remove or reduce any offending medications, exclude delirium and REM sleep behavior disorder as drivers, and the consider medication. First line is typically a trial of an AChEI such as donepezil or rivastigmine. 2nd we may consider an antipsychotic. Low dose Seroquel (quetiapine) is most commonly used. This is because of its low risk of EPS rather than efficacy. Indeed, it is largely ineffective. Sometimes other antipsychotic medications are carefully used at low doses such as olanzapine or aripiprazole. The antipsychotic with the most supporting data is clozapine at doses of 12.5-50mg daily, far lower than used in schizophrenia. It is licensed in Europe for psychosis in Parkinson's Disease but the EMA (FDA equivalent). Unfortunately, regular absolute neutrophil count monitoring is still required. Nuplazid (pimavanserin) is FDA approved for PDP and is a 5-HT2A inverse agonist and antagonist. It's effectiveness is probably equivocal. In general, high potency neuroleptics such as haloperidol are absolutely contraindicated in Parkinson's due to risk of severe EPS including NMS.