PHARMACOLOGIC TREATMENTS

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Psychopharmacology in Headache

Many classes of psychopharmacologic agents are used in the management of refractory headaches, both for the treatment of the headache disorder and for the treatment of co morbid psychiatric disorders. The rates of axis I psychiatric disorders such as major depression, dysthymia, bipolar I and II, generalized anxiety disorder, social phobia and obsessive-compulsive disorder are higher among patients with migraine and chronic migraine. These co morbidities complicate medical care due to increased morbidity, polypharmacy and side effects and require individualized assessment and management. An understanding of psychopharmacological agents is important to the neurologist as their actions can be beneficial, but their side effects and interactions may be devastating. When managing patients with headache disorders, the neurologist should have a deeper understanding of potential receptor effects, relative and absolute contraindications, whether blood levels can be measured, dosing strengths and regimens as well as potential length of treatment and long term efficacy.

The basic neuronal anatomy and neurotransmitters that are most likely involved in migraine are also involved in the pathogenesis of mood and anxiety disorders. The frontal lobe, anterior cingulate gyrus and deep limbic structures are involved in both headache and mood.

Serotonin, dopamine, and norepinephrine play key roles in the development of headache and associated nausea as well as mood and anxiety disorders. Interplay between these neurotransmitters and the inflammatory cascade of cytokinins involved in migraine may help explain epidemiologically supported comorbidities.

Antidepressants:

Antidepressant medications fall into select groups: tricyclic antidepressants (table 1), selective serotonin reuptake inhibitors (SSRIs) (table 2), serotonin and norepinephrine reuptake inhibitors (SNRIs) (table 3), monoamine oxidase inhibitors (MAOIs) (table 4) and atypical or other medications such as norepinephrine dopamine reuptake inhibitors (table 5). The relative efficacy of these medications with regards to both their antidepressant effect and antinociceptive has yet to be determined. Better evidence exists for the use of amitryptiline and venlafaxine for prophylactic treatment of migraine and are currently a level B recommendation. Fluoxetine may have better evidence than other SSRIs with regards to treatment of chronic headache but that may be because other large scale studies of alternative SSRIs have not been done or done definitively.

Table 1:

Tricyclic Antidepressants				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Blood levels can be obtained
Amitriptyline	Elavil	10, 25, 50, 75, 100, 125, 150 mg	10 – 300mg	+
Amoxapine		25, 50, 100, 150 mg	50 mg BID to 600mg/ day	-
Clomipramine	Anafranil	25, 50, 75 mg	25 – 250 mg	-
Desipramine	Norpramin	10, 25, 50, 75, 100, 150 mg	25 – 300 mg	+
Doxepin		10, 25, 50, 75, 100, 150 mg; 10mg/ mL	25 – 300 mg	-
Imipramine	Tofranil	10, 25, 50, 75, 100, 125, 150 mg	25 – 300 mg	+
Nortriptyline	Pamelor	10, 25, 50, 75; 10mg/5mL solution	25 – 150mg	+
Protriptyline	Vivactil	5, 10 mg	2.5 - 20mg TID	-
Trimipramine	Surmontil	25, 50, 100 mg	25 – 300mg	-

Selective Serotonin Reuptake Inhibitors				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Fluoxetine	Prozac, Serafem	10, 20, 40 mg, 20mg/5ml solution	10 – 80 mg qDay	All SSRIs now have a black box warning for possible increase in suicidal behavior in children, adolescents and young adults.
Sertraline	Zoloft	25, 50, 100 mg, 20mg/ml solution	25 – 200 mg qDay	
Fluvoxemine	Luvox	25, 50, 100, 150 mg ER	50 – 150mg BID	
Paroxetine	Paxil	10, 20, 30, 40; 12.5, 25 ER; 10mg/5ml	20 – 75mg qDay	
Citalopram	Celexa	10, 20, 40 mg; 10mg/ 5ml solution	20 – 60mg qDay	
Escitalopram	Lexapro	5, 10, 20 mg; 5mg/ 5ml solution	10 – 20mg qDay	

Serotonin Norepinephrine Reuptake Inhibitors				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Desvenlafaxine	Pristiq	50, 100 mg ER	50 – 100 mg	Predominant action on Serotonin
Duloxetine	Cymbalta	30, 60 mg	30 – 60 mg	
Venlafaxine	Effexor	25, 37.5, 37.5 ER 50, 75, 75ER, 100, 150ER, 225ER	37.5 – 300 mg	
Milnacipran	Savella	12.5, 25, 50, 100 mg	12.5 – 100 mg BID	Predominant action on Norepinephrine

Mono Amine Oxidase (MAO) Inhibitors				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Isocarboxazid	Marplan	10 mg	10 – 30 mg BID	Significant side effects, interactions and medicine and food restriction
Phenelzine	Nardil	15 mg	15 – 30 mg TID	
Selegiline Transdermal	Emsam	6, 9, 12 mg patch	6 – 12 mg daily	
Tranylcypromine	Parnate	10 mg	10 – 20 mg TID	

Other Antidepressants				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Buproprion HBr	Aplenzin	348, 522 ER	348 – 522 mg	Norepinephrine Dopamine Reuptake Inhibitors
Buproprion HCl	Wellbutrin, SR, XL Budeprion SR, XL	75, 100, 100ER, 150ER, 200ER (12 hr) 150 ER, 300ER (24 hr)	75 – 450 mg	
Maprotiline		25, 50, 75mg	25 – 75mg TID	Tetracyclic inhibits norepinephrine
Mirtazapine	Remeron, Remeron SolTab	15, 30, 45 mg	15 – 45 mg qHS	Tetracyclic antagonizes 5-HT2 and alpha2-adrenergic
Nefazodone	Serzone	50, 100, 150, 200, 250 mg	50 – 300 mg BID	Inhibits norepinephrine and serotonin and antagonizes 5-HT2
Trazodone		50, 100, 150, 300 mg	25 – 200 mg TID	Inhibits serotonin reuptake

There may be a small risk of serotonin syndrome in patients using either selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) in conjunction with triptan medications or other abortive medications such as tramadol. Only a small number of cases have been reported, but this may actually represent an underreporting of the true incidence . (Evans R. FDA Alert on serotonin syndrome with combined use of SSRI's and SNRI's and triptans: An analysis of the 29 case reports. *Med Gen Med*. 2007;**9**:48) Because of the black box warning on triptan medications this question comes up frequently in practice. While the evidence at hand suggests a minimal risk, it is an important to discuss with patients and may further determine the psychopharmacological strategies that are chosen.

Mood Stabilizers

The most common historical treatments for bipolar illness have included lithium and various antiepileptic medications. Several antidopaminergic agents have also been demonstrated to be effective in the acute phase.

Because of its efficacy in a psychiatric population, lithium has also been tested in the treatment of headache. To date, no studies have convincingly demonstrated effect in the treatment of migraine or tension type headache, but lithium has been found to be effective in the treatment of cluster headache.

Valproic acid increases GABA levels, enhances post synaptic response to GABA, causing neuronal hyper polarization and lowering the level of serotonin in the dorsal raphe nuclei. It appears to decrease aberrant neuronal firing and increases the seizure threshold. Valproic acid has consistently shown itself to be effective not only in the acute treatment of bipolar disorder, but also in maintenance therapy.

With regards to control of migraine, both sodium valproate and divalproex sodium has demonstrated efficacy. The evidence includes at least two placebo controlled studies for each of the drugs . (Yoon MS, Savidou I, Diener HC, Limmroth V. Evidence-based medicine in migraine prevention. Expert Rev Neurother. 2005 May;5(3):333-41) The extended release form of divalproex sodium also appears to have preventive efficacy (Freitag FG, Collins SD, Carlson HA, Goldstein J, Saper J, Silberstein S, Mathew N, Winner PK, Deaton R, Sommerville K; Depakote ER Migraine Study Group. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology. 2002 Jun 11;58(11):1652-9)

Carbamazepine was found to be effective with regards to migraine prophylaxis in one placebo controlled study, however other studies have failed to demonstrate efficacy above placebo.

Mood Stabilizers				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Carbamazepine	Tegretol	100 CH, 200 mg 100mg/ 5 ml soln	200 – 600mg BID	
Divalproex Sodium	Depakote Depakote ER	125, 250, 500mg 250, 500mg ER	125- 500 mg BID to TID	
Lamotrigine	Lamictal	25, 100, 150, 200mg 2, 5, 25 CH	25 – 200 mg qDay	
Lithium	Lithobid Eskalith	150, 300, 600 mg 300, 450 mg ER	300 – 900 mg BID	
Oxcarbazepine	Trileptal	150, 300, 600mg 300 mg/ 5 ml	300 – 1200mg BID	
Valproic Acid	Depakene Stavzor	125, 250, 500mg 250 mg/ 5 ml	250 – 500mg BID to TID	

Anxiolytics:

There are many options in the treatment of anxiety disorders. There are multiple non pharmacological methods that have been utilized including progressive relaxation training, hypnosis and autogenics, and cognitive behavioral therapy. There also are multiple pharmacological interventions. Most medications utilized are separated into benzodiazepines and non-benzodiazepine treatments. Among the non- benzodiazepine medications, most common are the selective serotonin reuptake inhibitors previously discussed.

Interestingly, one of the few remaining short acting barbiturates on the market is butalbital, which is found in several different headache preparations (e.g. Fioricet, Fiorinal, Esgic, and Esgic Plus.) Butalbital has a relatively short half life, and this may contribute to the general risk with medication overuse and rebound headaches.

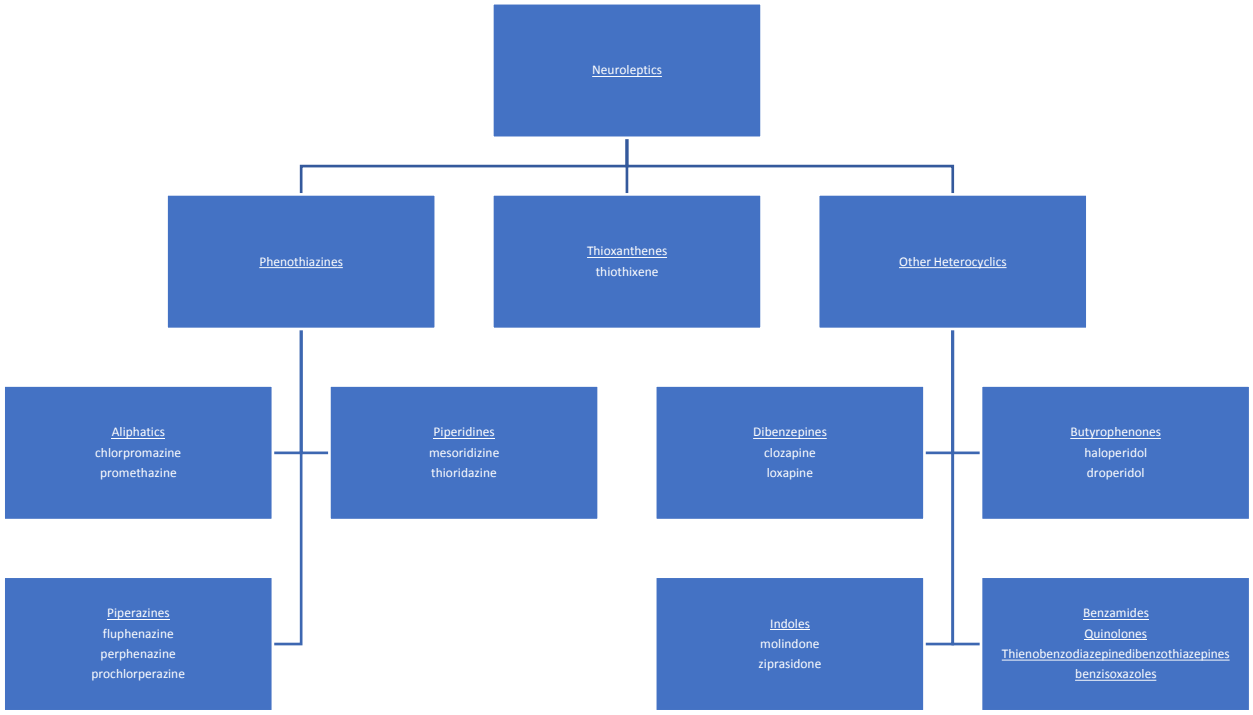
Non Benzodiazepine Anxiolytics				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Buspirone	Buspar	5, 7.5, 10, 15, 30 mg	7.5 – 30 mg BID	
Butabarbital	Butisol	30, 50 mg 30 mg / 5 ml	15 – 30 mg BID to TID	
Hydroxyzine	Atarax	10, 25, 50, 100mg 10mg/ 5 ml soln	50 – 100mg q6H	
Meprobamate		200, 400 mg	400mg TID - QID	
Pentobarbital	Nembutal	IM, IV	150 – 200mg	

Benzodiazepines				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Length of Action
Alprazolam	Niravam, Xanax, Xanax XR	0.25, 0.5, 1, 2 ODT, 0.5, 1, 2, 3ER, 1mg/ mL solution	0.25 BID - 2 mg TID	Short Acting and Rapid Onset
Midazolam	Versed	2 mg/ mL syrup; IM; IV	1 mg IV q 2-3 min	
Oxazepam		10, 15, 30 mg	10 – 30 mg TID	
Triazolam	Halcion	0.125, 0.25 mg	0.125 – 0.5 mg qhs	
Estazolam		1, 2 mg	0.5 – 2 mg qHS	Mid Length of Action
Lorazepam	Ativan	0.5, 1, 2 mg 2mg/ml solution IV, IM	0.5 qDay – 3 mg TID	
Temazepam	Restoril	7.5, 15, 22.5, 30mg	7.5 – 30mg qHS	
Chlordiazepoxide	Librium	5, 10, 25 mg	5 – 25 mg QID	Long length of Action
Clonazepam	Klonopin, Klonopin Wafer	0.5, 1, 2 mg; 0.125, 0.25, 0.5, 1, 2 ODT	0.125 – 6 mg TID	
Clorazepate	Tranxene SD, TranxeneT-tab	3.75, 7.5, 15 mg	3.75 – 20mg TID	
Diazepam	Valium	2, 5, 10 mg 5mg/5mL sol 5 mg/ mL nasal IM, IV	2 – 10 mg BID - QID	
Flurazepam	Dalmane	15, 30 mg	15 – 30 mg	

Antipsychotics

The antipsychotic medications, or neuroleptics, were predominantly derived from phenothiazine compounds that were used as synthetic dyes in Europe. Their general action is 'neurolepsis' or the suppression of spontaneous complex behaviors, vigilance, aggression, impulsivity and overactive response to stimuli.

The total group of neuroleptics breaks down to several subclasses. There are the phenothiazenes which split into aliphatics (such as chlorpromazine and promethazine), piperazines (including fluphenazine, perphenazine, trifluoroperazine and prochlorperazine), and piperidines (including mesoridazine and thioridazine.) There are thioxanthenes such as thiothixene, and other heterocyclics including dibenzepines (e.g. clozapine, loxapine), butyrophenones (e.g. haloperidol, droperidol), indoles (e.g. molindone, ziprasidone), benzamides, quinolones, thienobenzodiazepines, dibenzothiazepines, benzisoxazoles and others.



Dopamine Receptors

D1: Thalamus, Superior Chiasmatic Nucleus, Supraoptic nucleus, Arterial walls

D2: Peri Aqueductal Grey, Hypothalamus, Raphe Nuclei, basal Ganglia, Solitary nucleus, Dorsal motor vagal nucleus, presynaptic sympathetics

D3: Area postrema, Brainstem

D4: Brainstem

D5: Limbic regions, Basal Ganglia

The role of dopamine in migraine has been speculated about since 1977. It has been noted that stimulation of dopamine produces many effect similar to the migraine prodrome including yawning, mood changes, nausea and vomiting, gastrokinetic changes and hypotensive autonomic changes.

The neuroleptics also have a diverse effect on a range of other neurochemical messengers including serotonin, epinephrine and norepinephrine, acetylcholine and histamine. Some of these effects account for their particular side effects. These include hyperprolactinemia, dry mouth and eyes, hypotension, weight gain, metabolic syndrome, sedation, QTc prolongation and risk of sudden death, lowered seizure threshold and extra pyramidal movement disorders including tardive dyskinesia

1st Generation Antipsychotics				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Chlorpromazine	Thorazine	10, 25, 50, 100, 200 mg IM, IV	10 – 250mg TID to QID	
Fluphenazine	Prolixin	1, 2.5, 5, 10 mg 2.5/ 5 ml elixir	1 – 10 mg QID	
Haloperidol	Haldol	0.5, 1, 2, 5, 10, 20 mg	0.5 – 5mg TID reports up to 100mg/ day	
Loxapine	Loxitane	5, 10, 25, 50 mg	10 – 50mg BID	
Molindone	Moban	5, 10, 25, 50, 100mg	5 – 50 mg TID to QID	
Perphenazine	Trilafon	2, 4, 8, 16 mg	4 – 16 mg BID to QID	
Pimozide	Orap	1, 2 mg	1 – 2 mg qDay to BID	
Prochlorperazine	Compazine	5, 10 mg	5 – 10mg q6-8hr	
Thioridazine	Mellaril	10, 15, 25, 50, 100, 150, 200mg 30; 100mg / mL	50 – 200mg BID to QID (max 800mg)	
Thiothixene	Navane	1, 2, 5, 10, 20 mg	2 – 20 mg TID	
Trifluoperazine	Stelazine	1, 2, 5, 10 mg	1 – 20 mg BID	

2nd Generation Antipsychotics				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Aripiprazole	Abilify	2, 5, 10, 15, 20, 30mg 1 mg/ mL IM	2 – 30mg qDay	D2, 5-HT1A agonist; 5-HT2A antagonist
Clozapine	Clozaril FazaClo ODT	12.5, 25, 50, 100, 200mg	12.5 – 300mg BID (max 900mg/day)	Risk of agranulocytosis
Olanzapine	Zyprexa Zyprexa Zydis	2.5, 5, 7.5, 10, 15, 20mg	2.5 – 20 mg qDay	
Paliperidone	Invega	3, 6, 9 mg ER	3 – 12 mg qDay	
Quetiapine	Seroquel Seroquel XR	25, 50, 100, 200, 300, 400mg 25, 50, 100, 200, 300, 400mg ER	25 – 300 mg TID (max 800mg/day)	
Risperidone	Risperdal	0.25, 0.5, 1, 2, 3, 4 mg 1mg/ ml	0.25- 4 mg BID (max 16mg/ day)	
Ziprasidone	Geodon	20, 40, 60, 80mg	20 – 80 mg BID	

Attention Deficit and Hyperactivity Disorder

Very little is known about stimulant and non stimulant medications for attention deficit disorder and their effect upon migraine. While these drugs have headache listed as a side effect, there is no distinction as to whether this side effect is medication induced or acts as a trigger for migraine episodes.

Stimulants and Non Stimulants				
Generic Name	Trade Name	Available Dose Size	Reported Doses	Notes
Amphetamine/ Dextroamphetamine	Adderall Adderall XR	5, 7.5, 10, 12.5, 15, 20, 30; 5, 10, 15,20, 25, 30 ER	5 – 60 mg qDay - BID	
Atomoxetine	Strattera	10, 18, 25, 40, 60, 80, 100	10 – 100 mg qDay	
Dextroamphetamine	Dexedrine Procentra	5, 10, 15 mg ER	5 – 60 mg qDay	
Dexmethylphenidate	Focalin Focalin XR	2.5, 5, 10 mg; 5, 10, 15, 20 ER	2.5 – 10mg qDay - BID	
Lisdexamfetamine	Vyvanse	20, 30, 40, 50, 60, 70 mg	20 – 70 mg qDay	
Methylphenidate	Ritalin (LA, SR) Metadate (CD,ER) Methylin (ER) Daytrana	2.5, 5, 10, 20 18, 27, 36, 54 ER	2.5 – 15mg TID	

Basics of Psychopharmacology

1. Be certain of your diagnosis and your target symptoms.
2. Determine the most appropriate and simplest medication regimen.
3. Work collaboratively with the patient.
4. Set reasonable goals for treatment.
5. Start low and increase doses slowly to avoid adverse events.
6. Have a method for measuring treatment outcomes.
7. Foster collaboration with mental health professionals.