PHARMACY PHACTS

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Adjunctive Aripiprazole and Brexpiprazole in the Treatment of Major Depressive Disorder

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Aripiprazole (Abilify) is an atypical antipsychotic indicated as monotherapy for several psychiatric diagnoses, including bipolar I disorder and schizophrenia. Brexpiprazole (Rexulti) is another atypical antipsychotic approved for monotherapy in the treatment of schizophrenia. Mechanistically, both are D_2 and 5-HT_{1A} partial agonists, and both also carry an FDA indication for adjunctive therapy in major depressive disorder (MDD).

One study by Thase et al. examined the efficacy of aripiprazole as an adjuvant agent in MDD. Following antidepressant therapy for 8 weeks with escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine XR, patients were introduced to a double-blind randomized phase for 6 weeks during which they received adjunctive aripiprazole or placebo. Patients on aripiprazole were flexibly dosed between 2-20 mg daily with an initial dose of 5 mg/day. Patients taking concomitant CYP2D6 inhibitors, such as paroxetine and fluoxetine, were capped at 15 mg/day due to suspected increase in aripiprazole levels. The study measured baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores and Sheehan Disability Scale (SDS) scores for comparison after the 6 week double-blind randomization phase. The baseline MADRS for both groups was approximately 26, which indicates moderate depression. At the end of the double-blind phase, the patients receiving adjunctive aripiprazole showed a statistically significant reduction in MADRS (-8.7) compared to those taking an adjunctive placebo (-5.7). Although this endpoint reached statistical significance, the clinical significance of this finding is unclear. Patients on adjunctive aripiprazole also showed greater reductions in SDS scores at the endpoint (-1.2) compared to patients receiving the placebo (-0.6). The SDS scores showed significant improvements in social life and family life scores, but did not show statistically significant scores for work/school life. Remission rates were also significantly higher in the adjuvant aripiprazole group compared to placebo (25.7% versus 15.4%). At the end of the study, the mean daily dose of aripiprazole across all antidepressant therapies was 11.1 mg/day with a range of 2-20 mg/day. Overall, aripiprazole was well tolerated by most patients with the most common side effects being akathisia (25%), restlessness (12%), insomnia (8%), fatigue (8%), and anticholinergic side effects such as blurred vision (6%) and constipation (5%).

A similar study by Thase et al. reviewed the safety and efficacy of using a fixed dose of adjunctive brexpiprazole 2 mg in patients with MDD. During the first 8 weeks of the study, patients received a single-blind placebo adjuvant alongside standard antidepressant therapy, which included escitalopram, fluoxetine, paroxetine CR, sertraline, duloxetine, and venlafaxine XR. After the single-blinded period, the 6 week double-blind randomized phase began, assigning patients to the brexpiprazole adjuvant and placebo adjuvant treatment groups. Baseline MADRS (27.3 placebo, 26.9 brexpiprazole) and SDS (6.3 placebo, 6.0 brexpiprazole) scores were similar between the brexpiprazole and placebo

adjuvant treatment groups and were indicative of moderate depression. From baseline to week 6 of the double-blind phase, the mean reduction in MADRS was significantly greater in the adjuvant brexpiprazole group (-8.36) compared to the adjuvant placebo (-5.15). Patients taking adjunctive brexpiprazole also demonstrated a statistically significant greater reduction in mean SDS score (-1.35) compared to adjuvant placebo (-0.89). Although these endpoints reached statistical significance, their clinical significance remains unclear. The SDS scores showed improvements in social life and family life scores, but, like aripiprazole, were not statistically significant for work/school life. Brexpiprazole failed to reach statistical significance versus placebo in regard to remission rates. Brexpiprazole was generally well tolerated, with the most frequent side effects being weight gain (8%) and akathisia (7.4%), though they were reported as mild to moderate in severity by investigators. Mean body weight change was 1.64 kg for brexpiprazole and 0.36 kg for placebo, and clinically significant weight gain (≥7% increase from baseline) was seen in 4.8% of brexpiprazole patients versus 2.6% of placebo patients.

Overall, both studies were well-executed with few limitations. Both studies had adequate sample sizes, though it should be noted that both enrolled a majority of white female patients. The treatment phase was also relatively short, warranting further studies to confirm maintenance efficacy and safety. The same author conducted both studies, so they share similar disclosures and conflicts of interest. It should be noted that the studies were sponsored by the drug manufacturer, which poses a potentially confounding source of bias. Both medications are now FDA approved as an adjunctive treatment for MDD, with aripiprazole being the first to gain approval in 2007 followed by brexpiprazole in 2015. There is no compelling reason to prefer brexpiprazole over aripiprazole from an efficacy standpoint, although it may have fewer limiting side effects in some patients. In conclusion, aripiprazole and brexpiprazole have both shown efficacy and safety in MDD patients with inadequate response to antidepressant therapy alone.

FDA Approved Adjunctive Agents for Major Depressive Disorder

Drug	Indication	Dose Range	Maximum Dose	Cost[#] (30-Day Supply)
Aripiprazole (Abilify)	Major Depressive Disorder –Adjunct	Initial: 2-5 mg QD[*]; May adjust in increments of up to 5 mg/day at intervals of 1 week or more. Usual dosage range: 2-15 mg/day	15 mg QD[*]	~$900
Brexpiprazole (Rexulti)	Major Depressive Disorder –Adjunct	Initial: 0.5-1 mg QD[*] days 1-4, titrate to 2 mg QD[*] days 5-7, then to target dosage of 4 mg QD beginning on day 8	4 mg QD[*]	~$1330
Quetiapine (Seroquel)	Major Depressive Disorder –Adjunct	Initial: 50 mg QHS[*] Increase to 150 mg QHS[*] on day 3 Recommended dosage range: 150-300 mg/day	300 mg QD[*]	~$370

[*]QD: daily; QHS: nightly
[#]Cash price may vary slightly based on dose

References available upon request.

Epipen Expiration Dates

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Make note of the extended expiration dates on Epipens in the event you have a supply at home. On August 21, 2018, the Food and Drug Administration (FDA) announced they will extend the labeled expiration dates for specific lots of EpiPen 0.3 mg Auto-Injectors and their authorized generic versions by an additional 4 months. This decision comes in light of manufacturing constraints affecting the supply of these products. The FDA based their decision after the review of data provided by Pfizer (Meridian Medical Technologies, a subsidiary of Pfizer, manufactures the products). The expiration date extension comes at a period of increased demand with the back-to-school season beginning and is expected to temporarily improve patient access of this product while Pfizer works to stabilize the supply. The tables below show which lot numbers are included in this decision along with their new expiration dates.

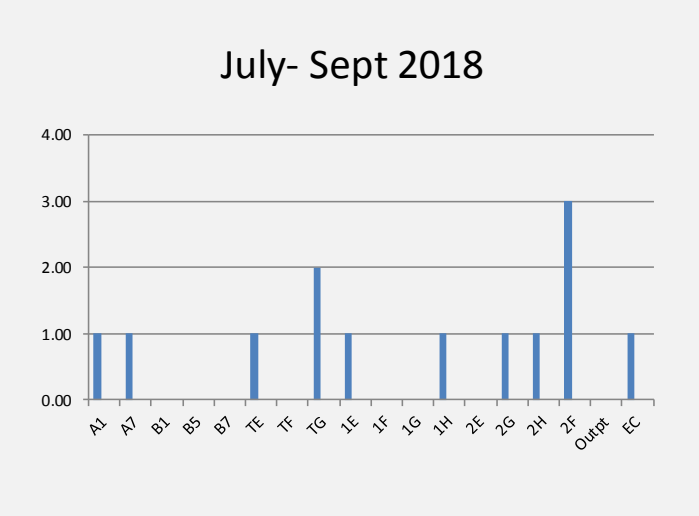
EpiPen 0.3 mg Auto-Injector Lot Numbers with Extended Expiration Dates
NDC 49502-500-02 appears on the box
NDC 49502-500-01 appears on the individual device within the box

Lot Number	Labeled Expiration Date	New Expiration Date
6GM480	Apr-18	Aug-18
6GM481	Apr-18	Aug-18
6GM503	Apr-18	Aug-18
6GM504	Apr-18	Aug-18
6GM506	Apr-18	Aug-18
6GM507	Apr-18	Aug-18
6GM512	Apr-18	Aug-18
6GM669	Apr-18	Aug-18
6GM599	May-18	Sep-18
6GM685	Jun-18	Oct-18
6GM766	Jun-18	Oct-18
6GM767	Jun-18	Oct-18
7GM026	Aug-18	Dec-18
7GM045	Aug-18	Dec-18
7GM048	Sep-18	Jan-19
7GM054	Sep-18	Jan-19
7GM164	Sep-18	Jan-19
7GM172	Sep-18	Jan-19
7GM173	Sep-18	Jan-19
7GM272	Sep-18	Jan-19
7GM191	Oct-18	Feb-19
7GM200	Nov-18	Mar-19
7GM201	Nov-18	Mar-19
7GM203	Dec-18	Apr-19
7GM204	Dec-18	Apr-19
7GM212	Dec-18	Apr-19
7GM213	Dec-18	Apr-19
7GM360	Dec-18	Apr-19
7GM361	Dec-18	Apr-19

References available upon request.

Adverse Drug Reactions (ADRs)

Number of ADRs reported



You may report an ADR by calling x3784 or entering the data into the Sunrise Allergies System.

Formulary changes

- Remove Terbinafine from formulary
  - Only 2 tablets used in over a year
- Rifaximin remains non-formulary
  - $38 per tablet; will only order if clinically necessary
  - In most cases, recommendation for use comes from outside GI specialist

Drug shortages

- Haldol tablets - 0.5mg, 1mg, 2mg
- Epi pen 0.3mg nationwide shortage
  - Teva brand on shortage; applies to certain Lot #
  - Sheppard Pratt Health System can give IM formulation if patient emergency