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Psychopharmacology: The 'Combo Pills'-Did it find its way into Practice?

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ABSTRACT *~ Fixed-dose combinations were, and still, quite in vogue in medical practice but for better or worse, did not gain a foothold in psychiatric prescriptions. Whilst briefing the merits and demerits of these formulations, authors herein provide a list of common psychotropic drug combinations on market, explaining the underneath psychopharmacological rationale.* Psychopharmacology Bulletin. *2025;55(2):80–84.*

'***Combo pills***', or fixed-dose combinations, typically combine ***two*** or ***more*** active drugs into a single formulation.[1] This was, and still, quite in vogue in medical practice but for better or worse, did ***not*** gain a foothold in psychiatric prescriptions.

On the one hand, these 'combo pills' simplified complex treatment regimens, a desideratum for complex-needs psychiatric patients typically on polypharmacy with poor insight, in order to ***enhance*** treatment adherence. Moreover, these gave the chance to intuitively exploit ***dynamic*** synergism/addition of drug combinations, ***kinetic*** interactions, or ***mitigate*** adverse drug reactions. At times, pharmaceutical industry dictates these forms in an attempt to *extend* proprietary rights and for sole marketing purposes when individual agents go off-patent.

On the other hand, these fixed combinations can often limit prescribers' capacity to tailor ***dosing*** regimens to individual patients in which case, pharmaceutical ***compounding*** remains a viable option to explore. Besides, a major flipside, for many of these preparations, dosing strengths are quite ***low*** and ostensibly ***subtherapeutic*** to address the original on-label indications for individual agents. These forms might pose challenges for manufacturers regarding multi-drug compatibility. Furthermore, if one component is contraindicated for a particular patient, these forms cannot t then be prescribed. Likewise, if unforeseen drug reaction happens, it could be difficult to pinpoint which agent is the main culprit.

In psychiatry, these forms abound, some are FDA regulated, whilst others are *not*. In the following section, we would go over a common list of these forms and meanwhile briefing the underneath psychopharmacological rationale.

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Limbitrol combines a low-dose of the tertiary amine tricyclic antidepressant (TCA) **amitriptyline**, a monoamine reuptake inhibitor, with the long-acting benzodiazepine (BDZ) **chlordiazepoxide**, a $GABA_A$ potentiator. Because of low-dose, this combo has been used short-term primarily for insomnia and co-thymia.

Motival combines a low-dose of the secondary amine TCA, **nortriptyline**, the more nor-adrenergic, and the conventional antipsychotic **fluphenazine**, a high- potent D_2 blockade. Albeit mechanistically appealing for ***psychotic depression***, again because of low-dosage, it is prescribed chiefly for co-thymia.

Deanxit combines the TCA, **melitracen**, and the conventional antipsychotic, **flupentixol**, akin to Motival (*vide supra*).

Cyclurad is a combination of **d-cycloserine**, a NMDA modulator, and the atypical antipsychotic **lurasidone**, is being investigated for acute suicidal ideation in bipolar depression.[2]

Symbayx is an ***FDA-approved*** combination of the SSRI antidepressant **fluoxetine** and the atypical antipsychotic, **olanzapine**, medium-potency $5HT_{2A}D_2$ blockade, for ***bipolar depression*** and ***treatment-resistant depression***. Synergism through $5\text{-}HT_{2c}$ antagonism with resultant Norepinephrine Dopamine Disinhibition in the prefrontal cortex underlies this combo.[3]

Dulane M, by an Indian manufacturer, incorporates **mecobalamin**, vit B_{12}, and the SNRI antidepressant duloxetine to complement its labelled indication for ***diabetic neuropathy***.

Zoline M, by an Indian manufacturer, combines the SSRI antidepressant **sertraline** with the long-acting BDZ **clonazepam**. This helps tiding over the first 2-week lag for sertraline to kick-in and complements anxiolytic actions. Since some evidence, albeit flimsy supports clonazepam add-on in OCD, for possible serotonergic actions, this combo can be a viable option for these cases as well.[4]

Risdone-Plus, again by an Indian manufacturer, combines the atypical antipsychotic **risperidone** with the anticholinergic **trihexphenidyl** to safeguard against extrapyramidal side effects whilst allowing going high on dose.

Neudexta, is an ***FDA-approved*** combination of the cough suppressant **dextromethorphan** (DXM), and the antiarrythmic **quinidine** for ***pseudobulbar affect*** (involuntary emotional expressive disorder). This is an exemplar of strategic use of kinetic DDIs. Since DXM is a CYP 2D6 substrate and quinidine is a strong 2D6 inhibitor, the latter serves to extend the former's half-life (cf. Auvelity).

Lybalvi This, a single-tablet combination of the atypical antipsychotic **olanzapine** (5–20 mg) and the mu-opiate receptor antagonist **samidorphan** (10 mg) was recently approved for adults with

schizophrenia/bipolar mood disorder. It was intended to provide the well-established efficacy of olanzapine whilst mitigating olanzapine-associated weight gain which was a major downside on clinical grounds. Based on ENLIGHTEN-1 and-2 studies, this combination has been associated with significantly less weight gain and smaller increases in waist circumference than olanzapine. The combination was well-tolerated while the antipsychotic efficacy of the combination was similar to that of olanzapine monotherapy.[5]

Namzarec is an ***FDA-approved*** combination of the NMDA antagonist **memantine** and the acetylcholine esterase inhibitor, **donepezil** for ***moderate to severe dementia due to Alzheimer's disease*** in patients already taking donepezil 10 mg/d.[6]

Auvelity is an ***FDA-approved*** extended-release combination of **dextromethorphan** (DXM) 45 mg and **bupropion** 105 mg- designated an RAAD (rapidly acting antidepressant) for adults with MDD. DXM is an uncompetitive NMDA receptor antagonist (cf. esketamine), sigma-1 receptor agonist and SRI. Bupropion, aminoketone, is an NDRI antidepressant and a potent CYP 2D6 inhibitor (for which DXM is a substrate) hence kinetically increasing levels and prolonging actions of DXM while dynamically additively boosting monoaminergic neurotransmission (cf. Neudexta for pseudobulbar affect). Approval was based on 2 trials (GEMINI and ASCEND).[7]

Librax combines the long-acting BDZ **chlordiazepoxide** with the antimuscarinic **clidinium bromide** and is commonly prescribed for ***irritable bowel syndrome*** and other functional gastro-intestinal disorders. Some psychiatrists use adjunctive Librax to ease out anxiety flare and gastrointestinal upset when initiating SSRIs.

Suboxone is a **sublingual** combination of **buprenorphine**, a partial μ opiate agonist and κ antagonist with **naloxone**, a μ antagonist. It is approved for ***opiate use disorder*** (***maintanence***). Idea behind incorporating naloxone is that naloxone has ***poor*** oral bioavailability, but if one tried to administer this comb ***intravenously***, naloxone would block any rewarding effects of buprenorphine and can precipitate withdrawal symptoms- a sort of ***aversive*** therapy.

Contrave is marketed for ***obesity*** as a fixed-dose combination of **naltrexone** (NTX), μ opiate antagonist, with the NDRI antidepressant **bupropion** (acting as an appetite suppressant) whilst NTX blocks reward/pleasure associated with food.[8]

Empatic combines the anti-epileptic **zonisamide** with the NDRI antidepressant **bupropion** (*vide supra*) for ***obesity***, where both medications cause weight loss.

Azstarys This new stimulant is ***FDA-approved*** for ADHD in those aged 6 and older and combines a fixed molar ratio of

30% **dexmethylphenidate** and 70% the prodrug- **serdexmethylphenidate** which is converted to dexMPH in lower GIT.[9]

Cobenfy has just been recently ***FDA approved*** for ***schizophrenia*** in adults. **Xanomeline** is a muscarinic receptor agonist with M1 and M4 preference. It has demonstrated antipsychotic properties in previous Alzheimer's disease and schizophrenia trials. It is devoid of dopamine blockade but causes significant cholinergic adverse events. **Trospium** is a peripherally acting muscarinic receptor antagonist with no central nervous system penetrability that reduces peripheral cholinergic effects of xanomeline.[10]

Qsymia combines the atypical amphetamine, **phentermine**, anorexogenic, with the antiepileptic **topiramate**, known to cause weight loss. It is indicted for those with **BMI ⩾ 30 kg/m^2** or those with **BMI ⩾ 27 kg/m^2** ***AND*** **metabolic risk**.

Filagra DXT Plus, by an Indian manufacturer, combines the phosphodiastrase-5 inhibitor aphrodisiac **sildenafil** with the SNRI antidepressant **duloxetine** (causing anorgasmia as a side effect) for ***erectile dysfunction*** and ***premature ejaculation***.[11]

Phex TC, by an Indian manufacturer, combines ***two*** conventional antipsychotics **chlorpromazine** and **trifluoperazine** with the anticholinergic **trihexphenidyl** to safeguard against EPS.

Codep 37, by an Indian manufacturer, combines the BDZ **chlordiazepoxide**, TCA **imipramine**, the conventional antipsychotic **trifluoperazine** and the anticholinergic **trihexphenidyl**.

Adderall is a mixed-amphetamine salts of **amphetamine sulphate, dextroamphetamine sulphate, amphetamine aspartate monohydrate, and, dextroamphetamie saccharate**. It is ***FDA-approved*** for ***ADHD*** and ***narcolepsy***. ✤

Disclosures

Authors declare no competing interests or financial affiliations.

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