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Monitoring Program

For Psychotropic Medications

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Purpose:

The North Dakota Medicaid Psychotropic Monitoring Program was created following the passage of the SUPPORT (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment) for Patients and Communities Act, which requires the state to have a program to monitor and manage the appropriate use of antipsychotic medications for children under 18 years of age, especially children in foster care. The state has further been encouraged to extend this program to all psychotropic medications, age groups, and living arrangements.

“Psychotropic medications” are medications intended to treat psychiatric disorders by affecting the central nervous system. Examples include, but are not limited to, anxiolytic agents, antidepressants, mood stabilizers, antipsychotics, hypnotics, and stimulants.

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Monitoring Program Interventions:

Medication Therapy Management (MTM)

ND Medicaid provides an opportunity for providers to get reimbursed for working with members who are having issues with their psychotropic medications, such as non-adherence, visits to the emergency room, or hospitalization. These cases can either be provider or department identified. Please see the Provider Manual for Pharmacy Medical Billing for more information on how to participate in this program.

Prospective Utilization Review:

ND Medicaid has many utilization review parameters in place for psychotropic medications including quantity limits, age and diagnosis verification, and/or therapeutic duplication. When medications are used outside of these set parameters, which are based on FDA and compendia-based information, a message will be sent to the pharmacy at the point of sale along with a rejection.

Educational messages are also sent back on paid on-label claims to supplement a pharmacists' clinical review at the time of dispensing.

Please see the following for more detailed information regarding prospective utilization review management tools as described below.

- Preferred Drug List (PDL)
- NDC Drug Lookup
- Coverage Rules on Medications

Quantity limits

ND Medicaid sets quantity limits on psychotropic medications. Quantity limits are used to ensure prescribing regimens are not needlessly complex to increase adherence as well as to prevent off-label higher than recommended doses.

- Administration Frequency and Half Life
- Lower than FDA Approved Dosing
- Booster Dosing

Age Verification

ND Medicaid sets age rules on all antipsychotics and stimulants, as well as various other psychotropic medications. Use of medications younger than an FDA approved or compendia supported age is not covered.

Medications have various dosage forms. Dosage forms can be specifically formulated to meet the needs for certain groups such as children who have not yet developed the ability to swallow a solid tablet or capsule. Age verification is also used to verify appropriate use of these dosage forms. For use in member groups that are aged 10 years or older and are unable to swallow, non-solid dosage forms can be requested by using the general PA form. Please see the Dosage Formulations section for more information on formulation properties.

Diagnosis Verification

ND Medicaid electronically verifies diagnosis on all antipsychotics, amphetamine stimulants, and various other psychotropic medications. This is done by electronic diagnosis code submission by the pharmacy at point of sale. A challenge can arise when a diagnosis is being evaluated but has not yet been added to a member's problem list. For urgent and emergency situations, detailed documentation may be necessary to evaluate for coverage of the medication, including assessment of the diagnosis according to the DSM and justification of the medication use. Use of medication outside of FDA approved or compendia supported diagnoses is not covered.

Therapeutic Duplication

ND Medicaid has therapeutic duplication rules on all psychotropic medications. The therapeutic duplications rules prevent use of multiple medications from overlapping mechanisms of action. Some medications can increase or decrease the metabolism of other medications resulting in higher or lower than expected therapeutic levels. Some significant drug interactions may reject prompting the pharmacist to discuss the drug interaction with the prescriber(s) to verify the benefit/risk has been evaluated.

Use of drugs that have drug interactions or have overlapping mechanisms of action can cause an increase of adverse effects. Please see the following sections for more information:

- Adverse Effects
- Drug Interactions

Underutilization

Medication adherence is important to the overall safety and efficacy of a drug. ND Medicaid sends back messages at the point of sale on all maintenance medications including psychotropic medications. If the member has not been adherence to their prescribed regimen, a message will be posted to the pharmacist noting how many days have been missed and adherence percentage. These messages serve as tools for counseling members on adherence and can be used to identify members eligible for MTM service.

Retrospective Utilization Review

The retrospective review program involves periodic examination of claims data and other records against compendia and peer reviewed literature monitoring for therapeutic appropriateness, overutilization and underutilization, appropriate use of generic products, therapeutic duplication, drug-disease contraindications, drug-drug interactions, incorrect drug dosage or duration of drug treatment, and clinical abuse/misuse and, as necessary, introducing remedial strategies, in order to improve the quality of care and to conserve program funds. The program also educates practitioners on common drug therapy programs with the aim of improving prescribing or dispensing practices.

Letter Campaigns

ND Medicaid provides around 400 monthly educational letters. Many of these letters involve topics related to psychotropic medications. A letter is sent to both the prescriber and pharmacy, with an opportunity to provide feedback on the usefulness of a particular intervention.

- Member specific letters relate to certain drug or disease related interactions, adverse effects, and recommended monitoring.
- Targeted interventional letters are topic focused and typically correlate with coverage rule implementation, guideline changes, or FDA precaution or warning statements. These letters are sent to providers that engage in the prescribing and/or dispensing of the medications affected by the identified topic.

Provider Education

Provider education is provided by both written and verbal presentation methods. Verbal presentations are given in one-on-one or group presentations and virtual or in person formats. Topics related to the use of psychotropic medications are frequently published and available for viewing by the public using the following links:

- Academic Detailing
- Newsletters

Chart Note Documentation:

Chart notes may be requested for review by ND Medicaid as part of this monitoring program. It is important that providers keep detailed documentation for the use of psychotropic medications. Clear records will also become an important part of a member's history and safety, especially during times of transition, whether it be a transition in clinic-based provider care, home or facility placement, or admission or discharge from a health care setting. It is important for providers and caretakers to know what the response was to medication trials, including if the trial was adequate in dose and duration, and rationale for why a medication was started or discontinued. Below are several areas to consider when documenting psychotropic medication utilization in chart notes.

Before Prescribing

- The following has been evaluated:
  - Any existing treatment or substance abuse that could be exacerbating the member's behavior
  - Potential benefits and risks of psychotropic medication weighted against the risks of untreated illness
  - The member and care team have received appropriate evidence-supported psychotherapeutic treatments and non-pharmacologic therapy for a length of time appropriate for effectiveness
  - Any environmental factors (e.g., in the home, placement or school setting) that could or should be addressed first

Starting a medication

Psychotropic medications should not be used for the purposes of discipline or chemical restraint, except as acutely necessary in true psychiatric emergencies. Long term consequences of prescribing psychotropic medications to children and adolescents are not completely understood.

- Medications within FDA-approved indications and dosages should be used when possible.
    - Widespread use in practice does not mean that “off-label” uses of medications are effective and safe.
- Initiate or change one medication at a time.
    - Start with the lowest possible dose and gradually increase the dose to effect
    - Multiple single medication trials may be necessary prior to considering combination therapy.

Informed Consent and Assent:

- Prescriber informs the child, family, and caregiver of the risks and benefits of the proposed treatment and alternative treatments, including absence of treatment. Information should be provided about the anticipated benefits of the medication, possible risks and side effects, the range of doses, initial effects to anticipate, what would constitute a reasonable trial, and medication adherence.

Providing justification:

- Targeted Symptoms
    - The targeted symptoms often are the behavioral manifestations of a child’s emotional and/or cognitive dysregulation.
    - Medications should be considered with care during events or situations which may be stressful or traumatic for a child, such as the initial removal from the home, or a change in placement.
- Clear rationale should be provided for choosing a particular medication as the most appropriate option at that time including:
    - Psychosocial interventions utilized with start dates and response
    - Psychotropic medications: specify the dosage and medication monitoring schedule
    - Alternative therapies that have been considered / ruled out
- Short- and long-term treatment goals: stated in ways that can be observed and measured on a regular basis by specified means.
- Estimated length of time for the following:
    - How soon medication effectiveness should be seen
    - How long the medication will be maintained

After prescribing:

Re-assessment of medication treatment:

- Periodic evaluation of treatment efficacy and tolerability should occur, including the following:
    - Are target symptoms well controlled in at least one of the child’s natural environments (home, school, daycare, placement, etc.)?
    - Are the medication dose and duration adequate?
    - Does the patient state that the medication is helpful?
    - Do the observed therapeutic benefits to date outweigh the potential risks?
    - Are there any medication adverse effects that indicate a need for tapering dosage and/or discontinuation?
        - Caution should be used before treating side effects with the addition of medication

    - Efforts are made to adjust medication dose to the minimum at which it remains effective and side effects are minimized.
- Include meaningful measures of psychosocial functioning such as:
    - Improved grades
    - Improved peer relationships at school
    - Ability to maintain work or home life

Challenges where additional documentation may be requested

*Not all-inclusive

Issue	Intervention
Off-label use of medication	Documentation of all previous trials and off-label justification. On-label trials are preferred to be completed, failed, or ruled out prior to off-label trials. Off-label prescribing must be supported by compendia strength of recommendation of at least IIb and strength of efficacy of IIa to be payable to ND Medicaid. The compendia used by ND Medicaid is IBM Micromedex® DRUGDEX®
Ongoing medication use to rule out or evaluate for a diagnosis	Documentation of ongoing assessment according to the DSM.
Co-occurring diagnoses	Documentation of medication selection evaluation including any exacerbation of co-occurring diagnoses and attempts to address all symptoms with the least number of medications and diagnoses.
Vague terminology	Documentation of clear descriptions of behaviors and thoughts. Non-specific language, such as mood instability, does not allow other practitioners and payers to understand the nature or extent of observed symptoms. Agitation is vague and not descriptive enough to represent an indication for medication. Please describe specific behaviors. Reserve medication usage for the treatment of disorders and not individual symptoms or natural psychosocial stressors and stimuli.
Initiation or change of more than one medication at a time	Preference for monotherapy should be considered whenever possible. Multiple medications in the same class should be reserved for when available monotherapy trials have been exhausted or ruled out. Document trials and justification for each option prior to implementing polypharmacy therapy. Change one medication at a time. Attempt to achieve target dose and duration prior to adding or switching to a new medication to avoid a scenario where it is unknown why improvement was or was not seen. Document urgent scenarios requiring multiple medication adjustments with justification.

Ineffective or partially effective medications	Each medication's need and effect should be clearly identified and documented, or discontinued, to avoid an increasing number of medications being used with unknown benefits.
Non-complete cross titrations	When a medication is being cross titrated to another medication and symptoms stabilize, concomitant use should not be continued indefinitely. A period of 3 months will be allowed to complete full cross over to the new medication.
Maintenance meds disguised as PRN use	If PRN meds are being used at regular intervals, that may indicate a need for initiation or adjustment of a maintenance schedule to target the underlying disorder causing the symptoms and should be considered when calculating the overall daily dose.

Outside of Utilization Management Requests

Off-label prescribing not supported by the compendia is not covered, however, in some cases, use of medication outside of electronic utilization review parameters may be appropriate in severe or urgent scenarios. A review for an override can be requested by:

- Calling ND Medicaid provider relations at 1-800-755-2604
- Submitting chart notes by fax to 701-328-1544
- Submitting a Prior Authorization Form
- Emailing medicaidpharmacy@nd.gov

Antipsychotic Therapeutic Duplication Requests

Doses can typically be increased quickly into a therapeutic range. Dose changes should be made with caution particularly in drugs with a longer half-life. With the delayed time to steady state and response, an impression may be given that an increase in efficacy was a result of a recent dose increase rather than the efficacy gained with elapsed time of a drug being at steady state within therapeutic range. Rapid increases in dose can also affect tolerability.

The time to initial response is typically between 2 and 4 weeks. Target doses are recommended to be given for at least 2 weeks prior to determining a no response or worsening response leading to a change in treatment. If a minimal response (≥ 20% reduction in symptoms) is not seen by 2 weeks, it is unlikely a much-improved response (≥50% reduction in symptoms) will be seen by 4 to 6 weeks.

If minimal or no response is seen, lifestyle consideration such as non-compliance and cessation or resumption of smoking should be ruled out as causes prior to adjusting medication regimen. If reported history of adherence is questionable, contacting pharmacy or payers for fill history or obtaining therapeutic levels may be beneficial.

If a higher therapeutic dose trial of 6 weeks results in a minimal or no response with adherence of at least 80%, a different antipsychotic should be considered. If after two antipsychotic trials of therapeutic dose, duration, and adherence; a clozapine trial is recommended. Clozapine should also be considered in cases where a response to antipsychotic treatment is seen, however significant impairment is still experienced. Clozapine is often underutilized. A trial of clozapine should not be delayed by multiple attempts at augmentation therapy or combination therapy.

Clozapine is an exception to general dosing guidelines as it requires very slow titration to minimize risk of side effects. A trial at target dose of 3 – 6 months is recommended prior to determining effectiveness treatment decisions.

Unsupported Requests:

Unsupported Use

Use outside of FDA approved or compendia supported diagnoses is not covered. Coverage may be considered for drugs that are considered standard of care, expert consensus, or are guideline supported. Use outside of these levels of evidence is considered investigational and is not covered. Individual studies in support do not provide enough evidence for coverage.

Examples of requests that are ***not covered:***

- Amantadine for mood modulation, autism spectrum disorder, or ADHD
- Aripiprazole to counteract weight gain from antipsychotics

Unsupported Combinations

Multiple drugs with the overlapping mechanisms of action should typically not be used together. This practice can increase the risk of adverse effects. Any increase in efficacy would likely be contributed to the overall increase in exposure to the therapeutic mechanism of action rather than the use of two individual drugs.

When a drug is utilized, it exhibits its entire range of therapeutic and adverse effects regardless of its intended use. Whenever possible, one drug should be used at the maximum tolerated dose needed to treat multiple symptom targets.

Characteristics of an individual drug should be considered when determining rationale for the observed response. Receptor affinity and selectivity may differ among drugs with the same overall mechanism of action resulting in different therapeutic and adverse effect potential.

Examples of requests that are ***not covered:***

- Clonidine dosed in the morning, and guanfacine dosed in the evening
- Aripiprazole for hallucinations and risperidone for aggression

Unsupported Dosing

The goal of an appropriate dose and interval is to achieve peak and trough levels of steady state within the therapeutic window so therapeutic benefit is obtained throughout the day and night.

Lower doses or less frequent intervals than approved results in drug exposure with risk of adverse effects without clinical benefit.

- Dosing lower than approved dosing results in not reaching the therapeutic window during steady state, or only reaching the therapeutic window during peak levels shortly after dosing.
- Dosing less frequent than approved intervals can result in elimination exceeding input for periods of the dosing interval which causes levels to dip below the therapeutic window for the

latter half of the dosing interval, or dose is completely eliminated before the next dose so a steady state is not reached.

Geodon (Ziprasidone)

Unbalanced dosing *is NOT covered*

- Ziprasidone is approved to be dosed twice daily with food in equal doses to target doses (≥120 mg/day)
- Ziprasidone should not be used daily at nighttime primarily for its sleep-inducing effects.
    - There is very little evidence to support daily night-time dosing because of the following characteristics:
        - Must be taken with food: Ziprasidone will not be adequately absorbed without at least a 500-kcal meal. It is not possible to compensate for this by increasing dose.
        - Short half-life: Half-life is 7 hours. Daily dosing will result in unbalanced levels throughout the day, likely including lower than efficacious blood levels by evening.
- Taking doses with food is essential, as absorption is increased two-fold in the presents of a meal g
    - When doses are taken in a fasted state, as often occurs with dosing at bedtime, the concentration achieved will likely not reach a therapeutic level adequate for antipsychotic efficacy and cannot be compensated for by dose increases.
- Steady state is achieved within 1 to 3 days with multiple per day dosing
- Side effects such as insomnia and agitation generally improve with dosage escalation and time.
    - Rapid dose escalation to target doses (≥120 mg/day) along with short term benzodiazepines may improve outcomes and efficacy as high doses are reached.

Desvenlafaxine (Pristiq)

25mg dose is *NOT* covered for maintenance therapy

The 25mg dose is covered for use for a gradual dose taper for discontinuation. In rare cases, upon request, the 25mg dose may be covered for a 30-day period for members with anxiety who are sensitive to overstimulation adverse effects.

50mg is the minimum therapeutic dose for adults. The 25mg dose is intended for a gradual reduction in dose when discontinuing the medication. Desvenlafaxine is not indicated for children.

Olanzapine

Multiple doses per day are *NOT* covered

Olanzapine has a half-life of 30 hours. The extended half-life allows it to be dosed daily. It reaches steady state in a week. Dosing olanzapine multiple times per day may result in higher doses and worse outcomes with increased side effects compared with daily dosing. Dose can be taken in the evening if it causes sedation.

Aripiprazole

Multiple doses per day are *NOT* covered

Aripiprazole has a half-life of 75 hours as well as an active metabolite which has a half-life of 94 hours. The extended half-life allows it to be dosed daily. In fact, the half-life is so long, efficacy is maintained with less than daily dosing so may be a good choice for nonadherent members.

Subtherapeutic 2 mg dose

The 2 mg dose is indicated for adjunct major depressive disorder and for use in pediatric indications. The 2mg dose will likely be subtherapeutic for adults being treated for bipolar disorder, borderline personality disorder, and schizophrenia. A typical starting dose for these disorders is 10mg.

Comparing Similar Psychotropic Medications:

Aripiprazole and Rexulti (brexpiprazole)

Cost	Tablet	Month	Year	Generic Availability
Aripiprazole	$0.13	$4	$48	Yes
Rexulti (brexpiprazole)	$39.00	$1,300	$14,200	No

Similarities:

- Aripiprazole and Rexulti (brexpiprazole) are clinically and structurally related.
- Extended half-lives
- Drug interactions within the CYP2D6 and CYP3A4 metabolism pathways
- Mechanism of action: Partial agonist of serotonin 5-HT-1A activity and dopamine D2 receptors, and antagonist of serotonin 5-HT-2A activity

Property	Aripiprazole	Rexulti (brexpiprazole)
Half-life	75 hours Active metabolite: 94 hours	91 hours
Interactions	CYP2D6 and CYP3A4	CYP2D6 and CYP3A4

Differences

Place in therapy:

- If a member is responding well to aripiprazole but is experiencing adverse effects, Rexulti (brexpiprazole) may be considered.

Adverse Effect	Aripiprazole	Rexulti (brexpiprazole)
Akathisia	2%-25%	4%-14%
Extrapyramidal movements	2% to 27.3%	5%-6%
Headache	10% to 27%	4% to 9%
Insomnia	8% to 18%	not reported
Nausea	8% to 15%	not reported
Restlessness	2% to 12%	not reported
Somnolence	6% to 26.3%	not reported

Receptor affinity:

- Rexulti (brexpiprazole) receptor affinity (compared to aripiprazole):

Receptor Action	Affinity	Effect

D2 (partial agonist)	Lower intrinsic activity	Lower potential for akathisia, insomnia, restlessness, agitation, and nausea
5-HT-2A (antagonist)	Higher affinity	May reduce akathisia
5-HT-1A (partial agonist)	Higher affinity	Potential benefits on depressive symptoms
α1 (antagonist)	Higher affinity	May reduce extrapyramidal symptoms (EPS), agitation, and sleep disturbances

Citalopram and Escitalopram

Cost	Tablet	Month	Year	Generic Availability
Citalopram	$0.03	$0.90	$10.80	Yes
Escitalopram	$0.03	$0.90	$10.80	Yes

Similarities:

- Citalopram is a mixture of two stereoisomers: R-citalopram and S-citalopram; Escitalopram is only one enantiomer: S-citalopram
- Similar half-lives (27- 32 hours)
- Low potential for drug interactions

Property	Description	Effect
Adverse Effects	nausea, vomiting, increased sweating, dry mouth, headache	Citalopram and escitalopram produce these adverse effects at similar rates
Receptor Affinity	Citalopram and escitalopram are among the most selective of the SSRI class	Citalopram and escitalopram do not have affinity for muscarinic, dopaminergic or norepinephrine receptors; Citalopram and escitalopram are SERT inhibitors

Differences

Place in Therapy:

- If a member is responding well to citalopram but is experiencing adverse effects, escitalopram may be considered.

Property	Citalopram	Escitalopram
Receptor Affinity	Mild antagonist at histamine 1 receptor	No effect at histamine 1 receptor
Drug Interactions	Mild effect at CYP2D6	No significant effect at CYP2D6

Adverse Effects:

- Citalopram is associated with dose-dependent QT interval prolongation; and is not recommended for patients with bradycardia, hypokalemia, hypomagnesemia, recent myocardial infarction, uncompensated heart failure

Risperidone and Paliperidone

Cost	Tablet	Month	Year	Generic Availability
Risperidone	$0.50	$15	$180	Yes
Paliperidone	$6.00	$200	$2,200	Yes

Similarities:

- Paliperidone (9-hydroxyrisperidone) is the active metabolite of risperidone with an hydroxyl group at 9
- Risperidone 4-6mg is similarly efficacious to paliperidone ER 6-12mg/day

Property	Description	Effect
Adverse Effects	Hyperprolactemia Extrapyramidal side effects	Paliperidone and risperidone produce these adverse effects at similar rates

Differences

Place in therapy:

- Adverse effect profile may be useful in guiding selection
- If CYP450 drug interactions or hepatic impairment are significant concerns, paliperidone may be a preferred choice

Property	Paliperidone	Risperidone	Effect
Release Mechanism	OROS ® technology	Immediate Release	Paliperidone produces less peak-to-trough variations in plasma levels and can be initiated at an effective dose
Metabolism	Four metabolic pathways and 60% is excreted unchanged in urine	Extensive metabolism via P450 2D6	Paliperidone does not have hepatic enzyme drug interactions or hepatic impairment dose adjustments. Risperidone has potentially significant drug interactions through the CYP 450 pathway
Adverse Effects	Tachycardia Sinus tachycardia Insomnia	Restlessness Anxiety Somnolence Nausea Akathisia	Differences in adverse effect profile might be a significant consideration
Receptor Affinity	Antagonist at D2 and 5HT-2A,	• Antagonist at D2 and 5HT-2A;	Risperidone has a higher affinity for 5-HT2A with a weaker affinity for

(in order strongest to weakest)	Antagonist at α1, α2, and H1	• Antagonism at α1, α2, and H1; • 5-HT1A, 5-HT1C, and 5-HT1D; • D1 and the haloperidol-sensitive sigma site; • Cholinergic-muscarinic, beta-adrenergic, and serotonin 5-HT1B and 5-HT3 receptor	D2 resulting in a higher 5-HT2A/D2 affinity ratio Paliperidone also affects mitochondrial protein expression and phosphorylation which may result in mood stabilization.
Food effect	Increase Cmax by 60% and AUC by 54%	None	Both drugs can be taken without regard to meals.
Dose Adjustments	Renal	Renal Hepatic Geriatric CYP450 interactions	Paliperidone does not require hepatic and CYP450 dose adjustments as risperidone does. Both require renal dose adjustments.

Venlafaxine and Desvenlafaxine

Cost	Tablet	Month	Year	Generic Availability
Venlafaxine	$0.05	$3.00	$36.50	Yes
Venlafaxine ER	$0.15	$4.50	$54.75	Yes
Desvenlafaxine ER	$0.52	$15.60	$189.80	Yes

Similarities:

- Desvenlafaxine is the active metabolite of venlafaxine (O-desmethylvenlafaxine) and is converted by the CYP450 2D6 pathway
- There are no significant differences in adverse effects or efficacy

Property	Description
Mechanism of Action	Inhibit the neuronal reuptake of serotonin and to a lesser extent norepinephrine
Elimination	Renally eliminated
Adverse effects	Adverse effects are similar in both medications. Interactions and genetic polymorphisms of CYP450 2D6 may result in more adverse effects in venlafaxine.

Differences

Place in therapy:

- If a member is responding well to venlafaxine but is experiencing adverse effects, desvenlafaxine may be considered especially if there is a known 2D6 interaction or genetic polymorphism. If member is not responding to venlafaxine, desvenlafaxine would not be a preferred alternative.
- If a member is not responding or tolerating desvenlafaxine, venlafaxine would not be a good alternative.

Property	Desvenlafaxine	Venlafaxine
Dose Titration	50mg is both the recommended starting dose and effective dose. 25mg is not an effective dose and not indicated for initial titration.	Requires titration to an effective dose.
Dose Related Response	At 50mg/day, desvenlafaxine inhibitors both serotonin and norepinephrine. Affinity does not change at 100mg/day	At low doses (75mg/day), venlafaxine blocks serotonin reuptake only acting like a SSRI, at high doses (150-225mg/day), both serotonin and norepinephrine reupdate is blocked.
CYP450 interactions	Maybe be preferred for significant 2D6 interactions or known genetic polymorphisms.	Reductions in 2D6 activity can cause decreased conversion to desvenlafaxine potentially resulting in decreased tolerability The effect on efficacy is unknown as venlafaxine and desvenlafaxine are equipotent.
Dose adjustments	Renal	Renal Hepatic

Antipsychotic Properties

Second generation antipsychotics (SGA) have different properties that require consideration when evaluating appropriateness for a member and if a trial is likely to be successful. The following properties of antipsychotics may be useful in determining the most clinically appropriate selection. The examples are primarily second-generation antipsychotics (SGAs); however, the same considerations apply to first generation antipsychotics (FGAs) and clozapine. The presented lists are not all inclusive and may not be up to date with rapidly changing information, so it is suggested to be used as examples for consideration. Please consult a reputable drug information resource for up-to-date information.

Absorption:

Rapid absorption (can be preferable in urgent situations):

- Saphris (asenapine) is the most rapidly absorbed
- Also quickly absorbed – Latuda (lurasidone) and Seroquel (quetiapine) IR

Slower absorption (can increase tolerability):

- Olanzapine, quetiapine ER, ziprasidone

Dosage Formulations

ODT formulations:

- Helpful for cheeking and trouble swallowing solid dosage forms
- Absorbed in GI tract after swallowed so availability and rate of absorption are identical to solid dosage form oral tablets
  - aripiprazole, clozapine, olanzapine, risperidone

Sublingual formulations:

- Helpful for cheeking and trouble swallowing solid dosage forms
- Absorbed transmucosally
  - Saphris (asenapine)

Immediate release injectable:

- Helpful for agitated and acutely psychotic patients
  - olanzapine and ziprasidone IM

Long-acting injectable:

- Helpful for patients unable to adhere to daily regimens
  - aripiprazole, olanzapine, paliperidone, and risperidone

Bioavailability

Food schedules need to be considered with some medications

Take with food:

- **Latuda (lurasidone) and ziprasidone**: Bioavailability may be increased two to three-fold in the presence of food
- Important Note: For ziprasidone, the decrease in bioavailability in a fasted state cannot be compensated for by increasing the dose

Do not take with a high fat meal:

- **Quetiapine ER:** Absorption is increased 50%

Adverse Effects

Side effects are a common limiting factor in usage of antipsychotics. Common side effects include weight gain, hypotension, sedation, anticholinergic symptoms, hyperprolactinemia, extrapyramidal symptoms (EPS), cardiac effects, etc.

Rates and severity of side effects vary among antipsychotics. The member's risk profile as well as the side effect profile should guide selection. Careful monitoring for the development of side effects is typically necessary.

The following are only some of the major side effects to consider while prescribing second generation antipsychotics (SGA).

Anticholinergic

More Side Effects	Less Side Effects
• cariprazine • clozapine • olanzapine • quetiapine	• aripiprazole • Caplyta (lumateperone) • Fanapt (iloperidone) • Latuda (lurasidone) • paliperidone • Rexulti (brexpiprazole) • risperidone • Saphris (asenapine) • ziprasidone

Extrapyramidal adverse effects:
akathisia, rigidity, bradykinesia, dysphagia, tremor, dystonic reactions

More Side Effects	Less Side Effects
• aripiprazole • Latuda (lurasidone) • olanzapine • paliperidone • risperidone (especially over 4 mg/day) • Rexulti (brexipiprazole) • Saphris (asenapine) • Vraylar (cariprazine) • ziprasidone	• Caplyta (lumateperone) • clozapine • Fanapt (iloperidone) • quetiapine

Metabolic adverse effects:
weight gain, impaired glucose metabolism, hyperlipidemia

More Side Effects	Less Side Effects
• clozapine • olanzapine • quetiapine esp. hyperlipidemia	• aripiprazole • Caplyta (lumateperone) • Latuda (lurasidone) • Rexulti (brexpiprazole) • Vraylar (cariprazine) • ziprasidone

Orthostatic hypotension
Mitigate by slowing dose titration or dividing dose into two or three smaller doses

More Side Effects	Less Side Effects

• clozapine • Fanapt (iloperidone)	• aripiprazole • Caplyta (lumateperone) • Rexulti (brexipraazole) • Latuda (lurasidone)

Prolactin elevation

More Side Effects	Less Side Effects
• paliperidone • risperidone	• aripiprazole (used to treat hyperprolactemia) • Caplyta (lumateperone) • clozapine • Latuda (lurasidone) • quetiapine • Rexulti (brexipiprazole) • Vraylar (cariprazine),

QT prolongation

More Side Effects	Less Side Effects
• ziprasidone	• aripiprazole • Caplyta (lumateperone) • Latuda (lurasidone) • Rexulti (brexipiprazole) • Vraylar (cariprazine)

Sedation

More Side Effects	Less Side Effects
• clozapine • olanzapine • quetiapine	• aripiprazole • Caplyta (lumateperone) • paliperidone

Metabolism

Most SGAs are metabolized by P450 systems in the liver which can lead to drug-drug interactions and dose adjustments.

Drug Interactions:

CYP 3A4 and 2D6 are the most common P450 systems to cause interactions in SGAs. Dose adjustments may be required when using with inhibitors and inducers of these enzyme pathways. When an inducer or inhibitor is discontinued, dose adjustments may likewise be required.

Less Drug Interactions:

- **Paliperidone:** 60% is excreted unchanged in the kidneys (only 10% is inactivated by hepatic enzymes)

- **Risperidone, olanzapine, and ziprasidone:** minimal drug interactions involving the CYP450 system and may be good choices when drug interactions are a concern
- **Saphris (asenapine) and ziprasidone** also experience fewer drug-drug interactions

More Drug Interactions:

See detailed information below

- Aripiprazole
- Clozapine
- Fanapt (iloperidone)
- Latuda (lurasidone)
- Quetiapine
- Rexulti (brexipiprazole)
- Vraylar (cariprazine)

Aripiprazole

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, etc.)	Decreased exposure and SGA dose should be doubled of its normal dose over 1 to 2 weeks
Strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.) with strong CYP3A4 inhibitors (itraconazole, clarithromycin, etc.)	Increased exposure and SGA should be started at a quarter of its normal dose

Rexulti (brexipiprazole)

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, etc.)	Decreased exposure and SGA dose should be doubled of its normal dose over 1 to 2 weeks

Strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.) with strong CYP3A4 inhibitors (diltiazem, verapamil, fluconazole, etc.)	Increased exposure and SGA should be started at a quarter of its normal dose

Latuda (lurasidone):

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and are contraindicated
Moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, verapamil, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, etc.)	Decreased exposure and are contraindicated
Moderate CYP3A4 inducers (e.g. bosentan, modafinil, etc.)	Decreased exposure and SGA dose should be increased after 7 or more days of concomitant treatment

Vraylar (cariprazine)

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose
Strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, etc.)	May inhibit the formation of the active metabolites of Vraylar (cariprazine) and are not recommended for concurrent use

Fanapt (iloperidone)

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and are contraindicated
Strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.)	Increased exposure and SGA dose should be reduced by half of its normal dose

Quetiapine

CYP450 interaction	Action
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and SGA dose should be reduced to one-sixth of its normal dose

Strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, etc.)	In chronic concomitant therapy (greater than 7 to 14 days), decreased exposure and SGA dose increases of up to 5-fold of its normal dose may be required to maintain control of symptoms

Clozapine

CYP450 interaction	Action
Strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	Increased exposure and SGA dose should be reduced to one third of its normal dose
Moderate/Weak CYP1A2 inhibitors (e.g. oral contraception, caffeine)	Increased exposure and SGA dose should be reduced if necessary
Strong CYP1A2 inducers (e.g. carbamazepine, phenytoin, St. John's wort)	Decreased exposure and not recommended for concurrent use. If concomitant treatment is necessary, clozapine dose may need to be increased.
CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, etc.) OR CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.)	Increased exposure and SGA dose should be reduced if necessary.

Interval Frequency and Half Life

A "half-life" is a property of a medication that informs how often a medication will need to be used throughout the day to produce a steady state.

An "active metabolite" may extend the duration of a drug beyond the parent compound's half-life.

Short Half-Life

Short half-lives allow for more rapid dose adjustments but require more frequent administration. A medication with a short half-life is dosed multiple time per day.

Oral Antipsychotics

Drug	Half-Life	Active Metabolite: Half-life
Risperidone	3 to 20 hours (oral)	9-hydroxyrisperidone: 21 to 30 hours ➢ Separately marketed as **Invega (paliperidone)**
Quetiapine IR	6 to 7 hours	norquetiapine: 12 hours (optional daily dosing)
Ziprasidone	7 hours	

Long half-life

Long half-lives allow for once daily dosing due to relatively stable levels but extend the time required to make dose adjustments or to clear completely when transitioning off medication.

Oral Antipsychotics

Drug	Half-Life	Active Metabolite: Half-life
Aripiprazole	75 hours (oral)	dehydroaripiprazole: 94 hours
Fanapt (iloperidone)	18 to 33 hours	P88: 26 to 37 hours P95: 23 to 31 hours
Latuda (lurasidone)	18 to 40 hours	
Olanzapine	30 hours	
Paliperidone	23 hours	
Rexulti (brexpiprazole)	91 hours	
Saphris (asenapine) Secuado (asenapine)	24 hours	
Vraylar (cariprazine)	2 to 4 days	desmethyl cariprazine (DCAR) 1 to 2 days didesmethyl cariprazine (DDCAR) 1 to 3 weeks

Long-Acting Injectable (LAI) Antipsychotics

BMI and Pregnancy

Pharmacokinetic differences are observed with BMI or pregnancy trimester for some LAI Antipsychotics. Please refer to reliable resource for specifics.

Injection Site

Cmax, Cmin, and Tmax differences are observed in some long-acting antipsychotic based on injection site, gluteal or deltoid. The extent (AUC) at which the drug is absorbed is typically the similar between the two injections sites, however, the rate of absorption (Tmax) may be quicker via the deltoid administration. The deltoid muscle has a smaller mass and higher perfusion. The differences may become less pronounced as steady state is reached, or more pronounced as dosing interval is increased. Please refer to reliable resource for specifics.

Abilify Maintena; Aristada 441mg

Deltoid or Gluteal.

Compared to gluteal administration, deltoid administration produces the following effects:

Tmax	Quicker	
Cmax	Higher	Can lead to adverse effects within days of injection

Therapeutic Considerations:

If adverse effects are experienced within days of injection, please consider these effects may improve after 4 injections. Alternatively, gluteal administration can be considered.

Invega Sustenna, Invega Trinza, Invega Hafyera

Initiation recommendations: 1st 2 injections should be deltoid administered

Maintenance recommendations: Deltoid or Gluteal

Compared to gluteal administration, deltoid administration produces the following effects:

Tmax	Quicker	
Cmax	Higher	Can lead to adverse effects within days of injection
Cmin	Lower	Can lead to breakthrough symptoms days before the next scheduled dose.

Therapeutic Considerations:

If adverse effects are experienced within days of injection or breakthrough symptoms are experienced days before the next scheduled dose, please consider a gluteal administration trial.

Risperdal Consta

Deltoid or Gluteal.

Deltoid site injections are bioequivalent to gluteal site injections.

Antipsychotic Initiation and Missed Doses Protocols

Due to extremely long half-lives, many LAI antipsychotics require loading doses or oral supplementation to maintain therapeutic antipsychotic concentrations during initiation and following a missing dose. Oral antipsychotics of the same active ingredient must also be used prior to LAI antipsychotics to assess tolerability.

Each LAI antipsychotic has its own recommended protocols for initiation and missing doses. Please use reputable references for these situations and use the following as a guide of situations requiring supplementation.

Abilify Maintena

Initiation:

- Requires 14 days of oral aripiprazole (or another antipsychotic if they are known to be tolerant to aripiprazole) after initial injection

Missed Dose:

Dose Missed	Time Since Missed Dose	Instructions
2nd or 3rd dose	> 5 weeks	Supplement oral aripiprazole for 14 days with the next administered injection.
4th dose +	> 6 weeks	Supplement oral aripiprazole for 14 days with the next administered injection

Aristada

Initiation:

- Requires 21 days of oral aripiprazole after initial injection

OR

- Aristada Initio injection + aripiprazole 30mg oral (one dose) within 10 days of the first Aristada injection

Missed Dose:

Aristada Dose	Time since last dose	Time since last dose
441 mg	> 6 and ≤ 7 weeks	> 7 weeks
662 mg	> 8 and ≤ 12 weeks	> 12 weeks
882 mg	> 8 and ≤ 12 weeks	> 12 weeks
1064 mg	> 10 and ≤ 12 weeks	> 12 weeks
Instructions	Supplement 7 Days of Oral Aripiprazole **OR** Re-initiate with a Single Dose of ARISTADA INITIO	Supplement with 21 Days of Oral Aripiprazole **OR** Re-initiate with a Single Dose of ARISTADA INITIO + a Single Dose of Oral Aripiprazole 30 mg

Invega Sustenna

Initiation:

- No oral required
- Injection schedule: 234mg Day 1, 156mg Day 8

Missed Dose:

- No oral required

Dose Missed	Time Since Missed Dose	Instructions
2nd dose (Day 8 156mg Dose)	< 4 weeks	Administer 3rd injection of 117mg 5 weeks after 1st injection (regardless of timing of 2nd dose)
	4 to 7 weeks	Administer 156mg dose ASAP and another 156mg dose 1 week later
	>7 weeks	Restart initiation – 234mg Day 1, 156mg Day 8
3rd dose +	>6 weeks to 6 months	**Dose 234mg:** Administer 156mg dose ASAP and another 156mg dose 1 week later
		Other doses: Resume previous dose
3rd dose +	>6 months	Restart initiation – 234mg Day 1, 156mg Day 8

Invega Trinza

Initiation:

- No oral required
- Use only after Invega Sustenna at next scheduled dose.

Missed Dose:

- No oral required

	Time Since Missed Dose	Time Since Missed Dose
Dose of Invega Trinza	> 4 months to 9 months	> 9 months
273 mg	Day 1 and Day 8: 78 mg	Treat with Invega Sustenna for at least 4 months
410 mg	Day 1 and Day 8: 117 mg	

546 mg	Day 1 and Day 8: 156 mg	
819 mg	Day 1 and Day 8: 156 mg	

Invega Hafyera

Initiation:

- No oral required
- Use only after Invega Sustenna or Invega Trinza at next scheduled dose.

Missed Dose:

- No oral required

	Time Since Missed Dose	Time Since Missed Dose	Time Since Missed Dose
Dose of Invega Hafyera	6 months 3 weeks to < 8 months	8 months to 11 months	>11 months
1092 mg	**Day 1:** 156 mg of Invega Sustenna **1 month after Day 1:** Resume dose of Invega Hafyera	**Day 1:** 156 mg of Invega Sustenna **Day 8:** 156 mg of Invega Sustenna **1 month after Day 1:** Resume dose of Invega Hafyera	Treat with Invega Sustenna for at least 4 months
1560 mg	**Day 1:** 234 mg of Invega Sustenna **1 month after Day 1:** Resume dose of Invega Hafyera	**Day 1:** 156 mg of Invega Sustenna **Day 8:** 156 mg of Invega Sustenna **1 month after Day 1:** Resume dose of Invega Hafyera	

Risperdal Consta

Initiation:

- Requires 21 days of oral risperidone after initial injection

Missed Dose:

Dose Missed	Time Since Missed Dose	Instructions
2nd or 3rd dose	N/A	Reinitiate with 21 days of oral risperidone with the next administered injection.
4th dose +	≤ 6 weeks	Resume normal dose
	> 6 weeks	Reinitiate with 21 days of oral risperidone with the next administered injection.

Zyprexa Relprevv

Initiation:

- No oral required

Missed Dose:

- No oral required

Dose Missed	Time Since Missed Dose	Instructions

2nd or 3rd dose	N/A	Reinitiate with loading instructions for the first 8 weeks
4th dose +	≤ 2 months	Resume normal dose
	> 2 months	Reinitiate with loading instructions for the first 8 weeks

Genetic Testing

Genetic variants cause significant difference in half-lives and serum levels in aripiprazole, Rexulti (brexpiprazole), clozapine, and Fanapt (iloperidone). Generally, drugs with genotype variant consequence can still be used but doses may have to be adjusted for expected levels.

Drug	Genetic Variant	Action
Aripiprazole Rexulti (brexipiprazole)	CYP2D6 poor metabolizers	start dose at half dose
	CYP2D6 poor metabolizers who are taking strong or moderate CYP3A4 inhibitors (rifampin, phenytoin, carbamazepine, diltiazem, fluconazole, verapamil, etc.)	start at quarter dose
Fanapt (iloperidone)	CYP2D6 poor metabolizers	start at half dose
Clozapine	CYP2D6 poor metabolizers	may need dose reduction

Genetic Testing

CYP2D6: Genotyping has not yet demonstrated clinical utility and therefore is **not covered**.

When pharmacogenomic testing is utilized outside of coverage, it is important to correctly interpret the results.

Tests commonly report descriptors such as variability in drug levels or side effects. These results should generally not be interpreted as a need to exclude a medication from therapy, particularly if a member is already on the medication or is otherwise indicated to trial the medication.

Typically, the results simply are meant to inform when increased monitoring or caution may be warranted when a dose is initiated or titrated. Monitoring serum drug levels is an effective alternative approach.

Booster Dosing

Medications that reach steady state:

Steady state is a concentration level that is reached in most maintenance medications where the blood level stays within therapeutic limits regardless of dosage, number of doses, or dosing interval when the rate of drug input and drug elimination are equal. This occurs in 5 elimination half-lives of the drug.

- A booster IR dose does not appreciably change the steady state concentration versus achieving the same daily dose with XR alone.
- Loading doses are useful if a drug has a long half-life and it is desirable to reach steady state sooner than 5 half-lives.
- Dosing with XR alone provides decreased fluctuation in plasma concentrations and an easier administration schedule. These formulations are developed to improve adverse effects and compliance.

Booster Dosing is NOT Covered

In the following cases, there is no evidence to support a dosage regimen combining immediate release and extended release and the practice undermines the benefits of using an extended-release product.

Seroquel XR (Quetiapine):

Booster dose is NOT covered

- Steady state is achieved within 2 days of dosing.
- Release is over 24 hours and bioequivalent to dosing of immediate release twice per day.
- Recommended dosing is to take dose daily in the evening. Post dose sedation may occur.

Wellbutrin SR / XL (Bupropion):

Booster dose is NOT covered

- Steady state is achieved within 8 days of dosing.
- Once daily bupropion (XL) is bioequivalent to two times per day bupropion (SR) and three times per day bupropion (IR).
- Once daily bupropion (XL) should be taken in the morning to avoid insomnia.

Effexor XR (Venlafaxine)

Booster dose is NOT covered

- Steady state is achieved within 3 days of dosing.
- Once daily venlafaxine (XR) is bioequivalent to twice daily dosing of venlafaxine (IR).
- Once daily venlafaxine (XR) is associated with less nausea and dizziness at initiation.

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ADHD Medications

Booster dose is NOT covered

- Adderall XR (Mixed Salts of a Single-Entity Amphetamine Product)
- Adhansia XR (Methylphenidate)
- Adzenys XR ODT / Adzenys ER (Amphetamine Suspension, Extended Release)
- Aptensio XR (Methylphenidate)
- Cotempla XR-ODT (Methylphenidate)
- Daytrana (Methylphenidate)
- Dyanavel XR (amphetamine suspension, extended release)
- Jornay PM ER (Methylphenidate)
- Mydayis (Mixed Salts of a Single-Entity Amphetamine Product)
- Vyvanse / Vyvanse Chewable (Lisexamfetamine)

Booster dose is covered

- Concerta (Methylphenidate)
- Focalin XR (dexmethylphenidate)
- Metadate CD (Methylphenidate)
- Ritalin LA (Methylphenidate)
- Quillivant XR / Quillichew ER (Methylphenidate)

Adderall XR (Mixed Salts of a Single-Entity Amphetamine Product)

Booster dose is NOT covered

Characteristics

- Has comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL (immediate release) twice daily administered 4 hours apart
- Time to peak is 7 hours.
- **Total Duration:** 8 to 10 hours

Special Consideration:

- Release is pH dependent and proton pump inhibitors may result in an excessive response shortly after administration and a diminished response at the end of the dosing interval. Proton Pump Inhibitors are not covered concurrently.

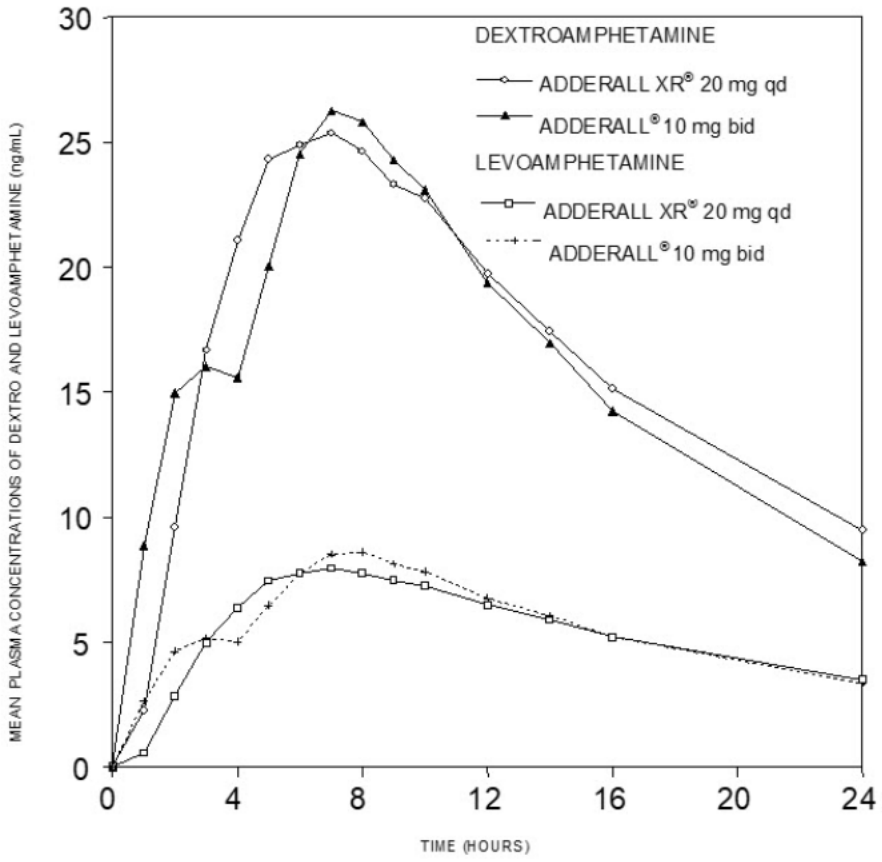


Figure 1 Mean d-amphetamine and l-amphetamine Plasma Concentrations Following Administration of ADDERALL XR 20 mg (8 am) and ADDERALL (immediate-release) 10 mg Twice Daily (8 am and 12 noon) in the Fed State.

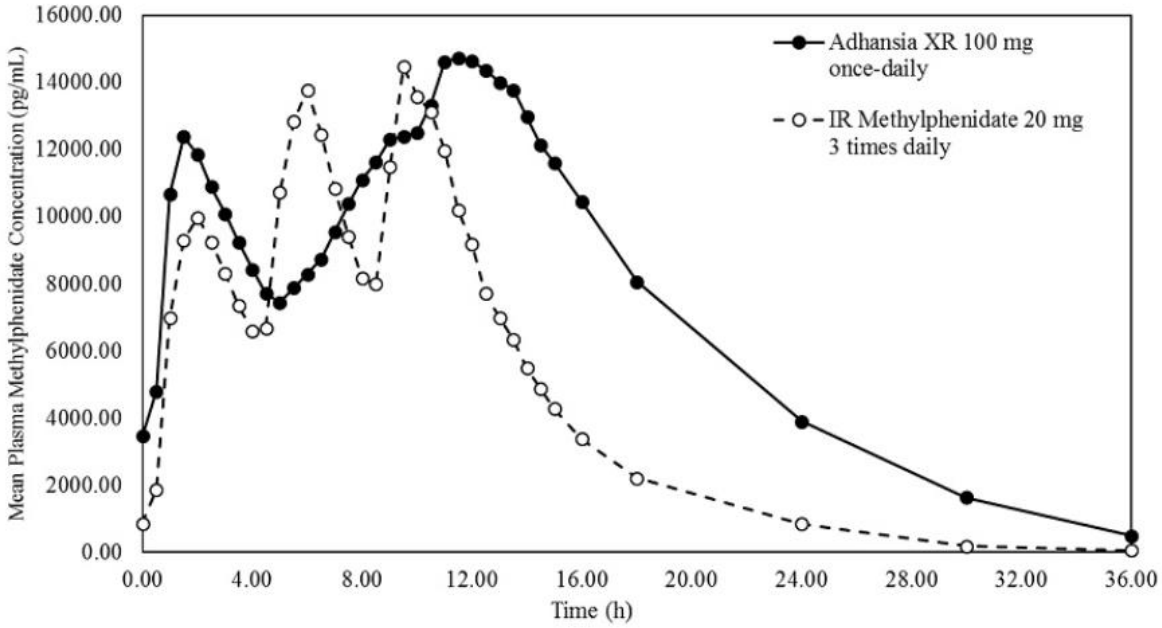
Adhansia XR (Methylphenidate)

Booster dose is NOT covered

Characteristics

- Has a relative bioavailability of methylphenidate three times daily administered every 4 hours
- The peak is biphasic, with the first peak occurring 1.5 hour after dosing, followed by a gradual decrease for 4 to 6 hours, followed by a gradual increase resulting in a second peak at 12 hours.
    - 20% immediate release
    - 80% extended release
- **Total Duration:** 16 hours

Figure 1: Mean Concentration-Time Profiles for d,l-Methylphenidate on Day 5 After Daily Dosing



Adzenys XR ODT / Adzenys ER (Amphetamine Suspension, Extended Release)

Booster dose is NOT covered

Characteristics

- Single peak occurs 5 hours after dosing
  - 50% immediate release
  - 50% extended release

Figure 1: Mean Concentration of D-Amphetamine and L-Amphetamine vs Time for ADZENYS XR-ODT (18.8 mg) and Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules (MAS ER 30 mg) in the Fasted State

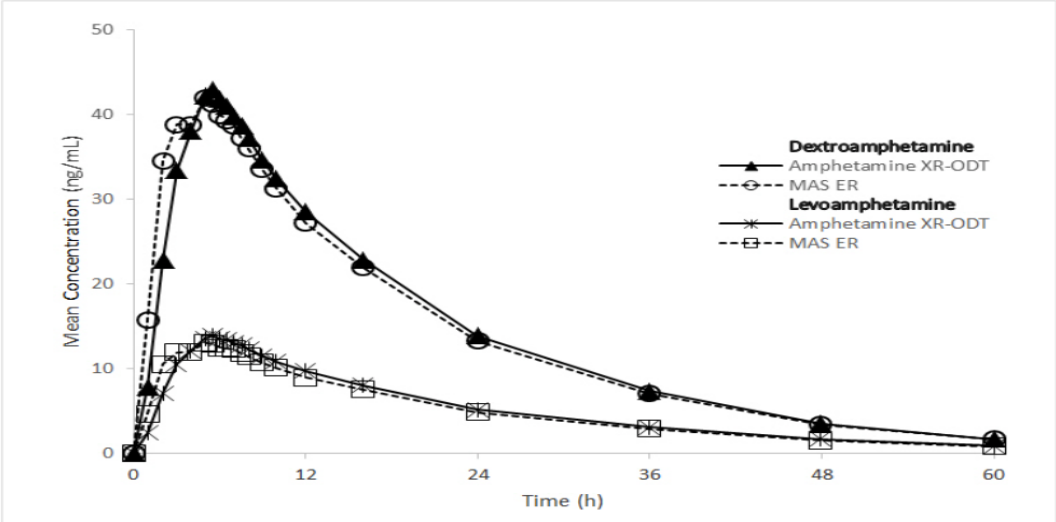
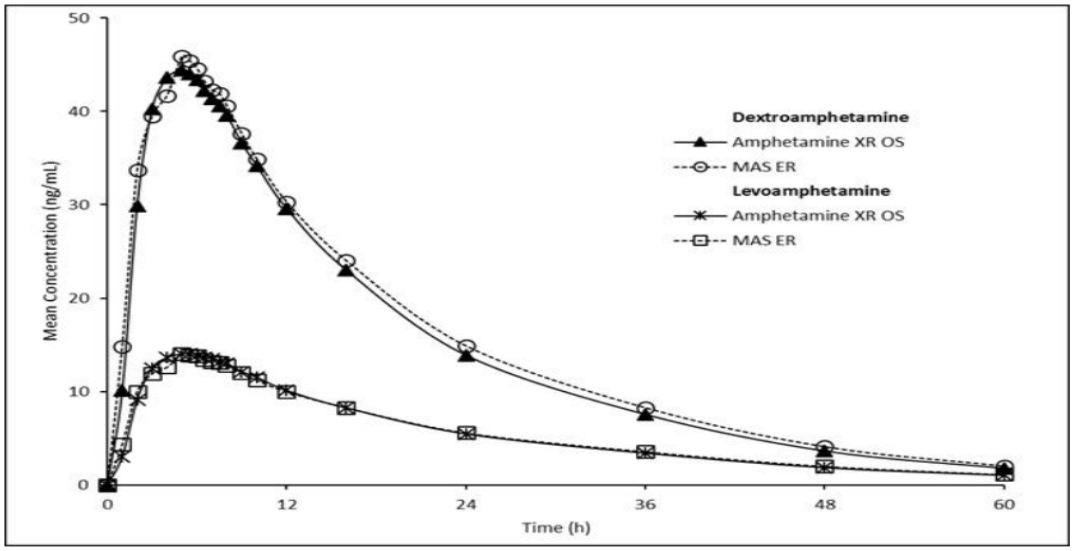


Figure 1: Mean Concentration of *D*-Amphetamine and *L*-Amphetamine vs Time for a 15 mL Dose of ADZENYS ER (18.8 mg amphetamine base equivalent) and Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules (MAS ER 30 mg) in the Fasted State



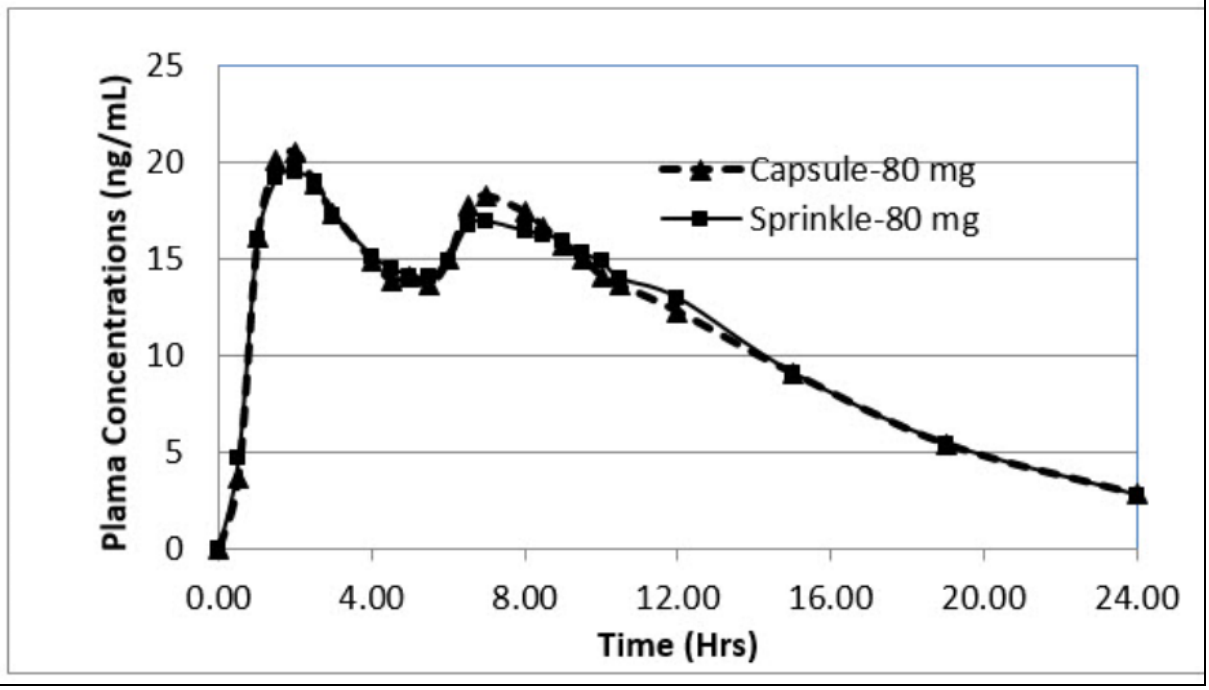
Aptensio XR (Methylphenidate)

Booster dose is NOT covered

Characteristics

- Has a relative bioavailability of methylphenidate three times daily administered every 4 hours
- The peak is biphasic, with the first peak occurring 2 hours after dosing, followed by a gradual decrease for 4 to 6 hours, followed by a gradual increase resulting in a second peak at 8 hours.
    - 40% of active compound released in the morning
    - 60% of active compound released in the afternoon
- **Total Duration:** 12 hours

Figure 1: Mean *d,l*-Methylphenidate Plasma Concentration-Time Profiles following 80 mg Administered as Capsule and Sprinkle Dose in Healthy Adults



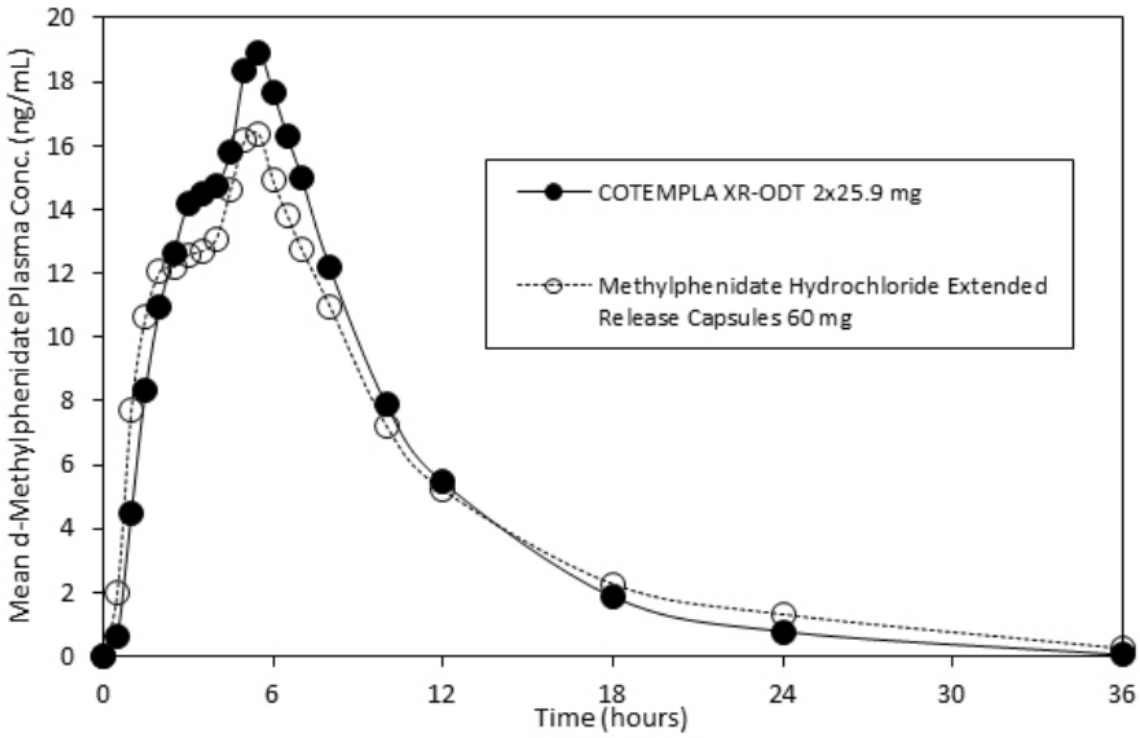
Cotempla XR-ODT (Methylphenidate)

Booster dose is NOT covered

Characteristics

- Peak levels are reached at about 5 hours after dosing
- **Total Duration:** 12 hours

Figure 2: Mean *d*-Methylphenidate Plasma Concentration-Time Profiles After Administration of COTEMPLA XR-ODT or Methylphenidate Hydrochloride Extended-Release Capsule in Healthy Volunteers Under Fasted Conditions



Daytrana (Methylphenidate)

Booster dose is NOT covered

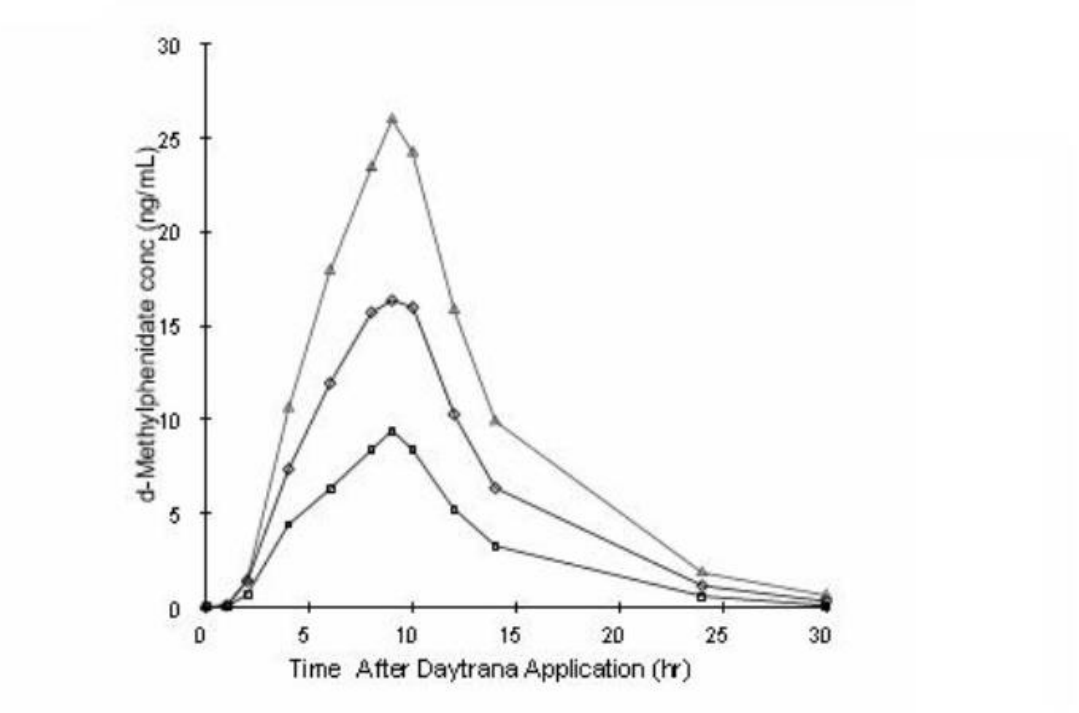
Characteristics

- Peak levels are reached at about 10 hours after first administration, and 8 hours after subsequent administration when worn up to 9 hours
- Transdermal absorption may increase with repeat dosing with steady state being achieved at 14 days of dosing
- Continued distribution may occur from the skin after patch removal
- **Total Duration:** 12 hours or 3 hours after patch removed[2]

Special Considerations:

- When Daytrana is applied to inflamed skin or heated, the rate and extend of absorption are significantly increased with C_{max} and AUC up to 3-fold higher.

FIGURE 1 Mean Concentration-time Profiles for d-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of d,l-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-Hour Patches



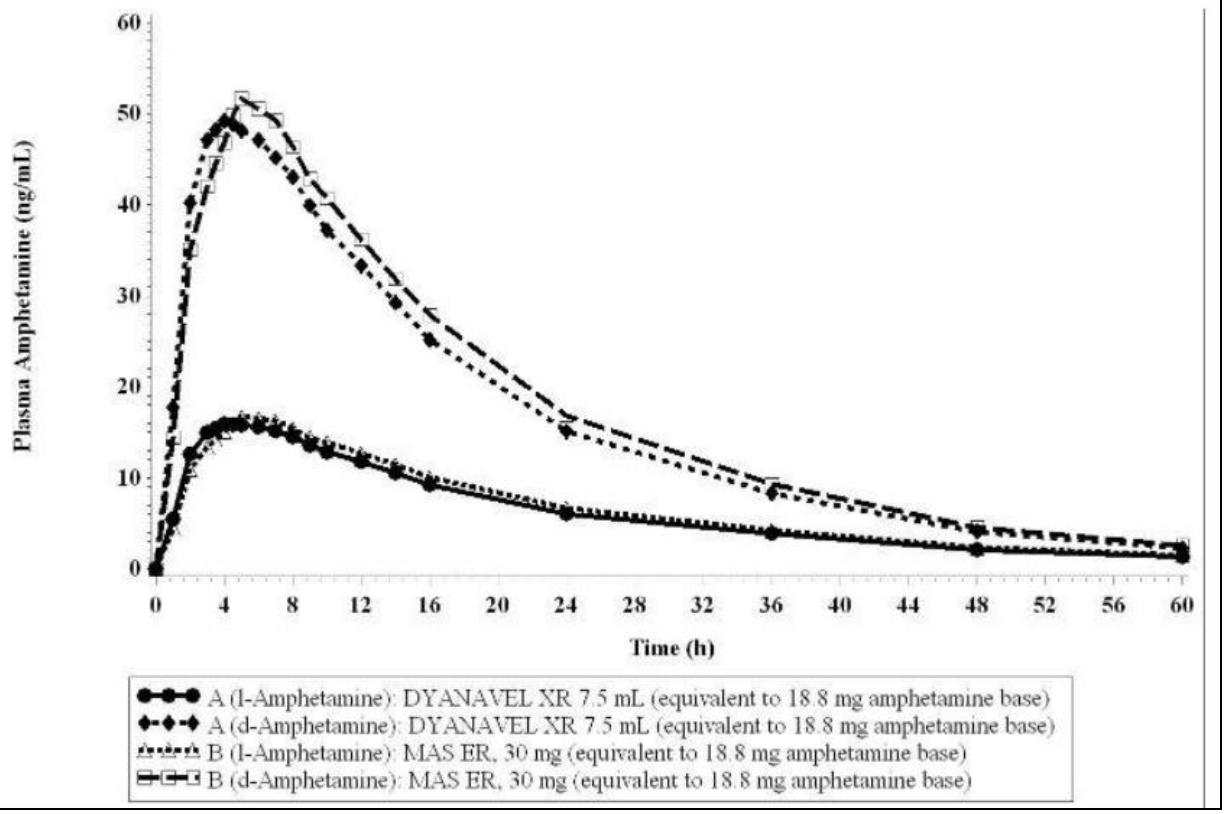
Dyanavel XR (amphetamine suspension, extended release)

Booster dose is NOT covered

Characteristics

- Single peak occurs 2-7 hours after dosing
- **Total Duration:** 13 hours

Figure 1. Mean *d*- and *l*- amphetamine Plasma Concentration-Time Profile Following Administration of a Single Dose (18.8 mg amphetamine base) of DYANAVEL XR and MAS ER Under Fasting Conditions

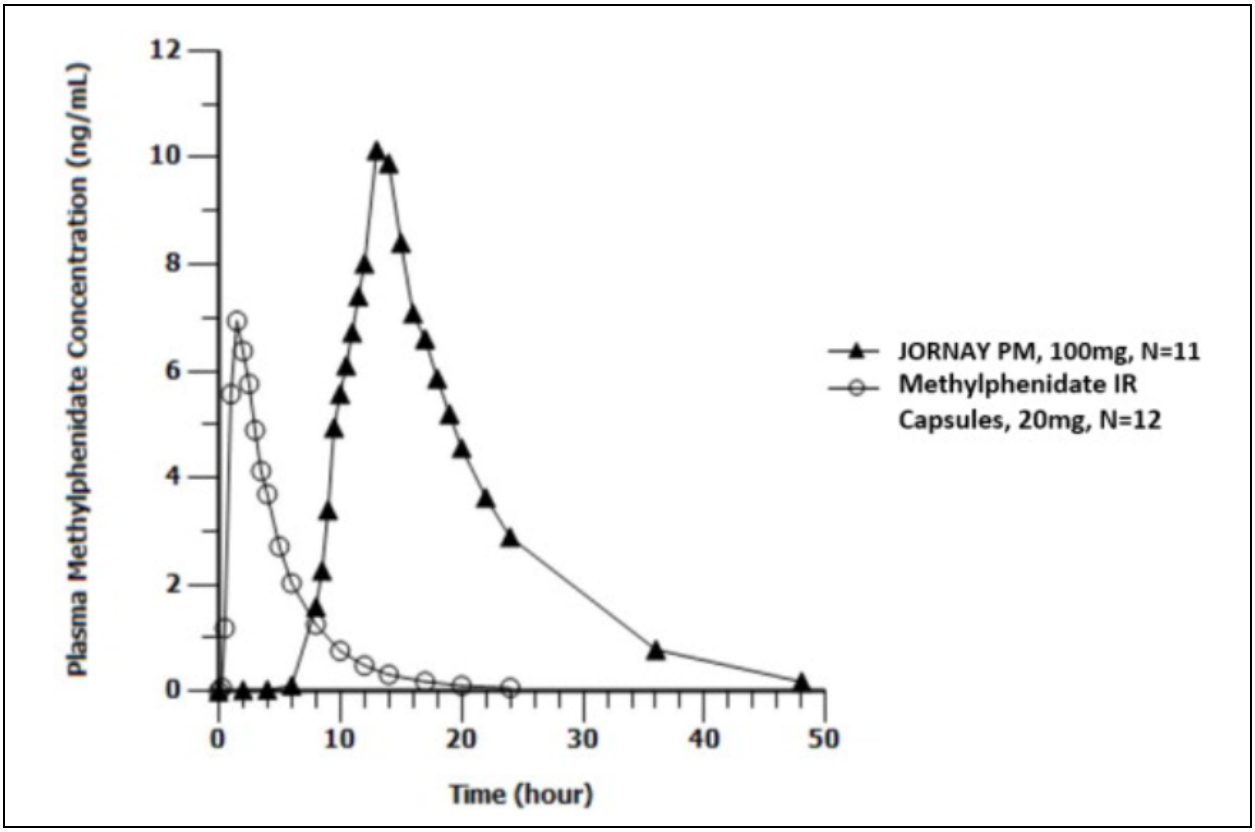


Jornay PM ER (Methylphenidate)

Booster dose is NOT covered

Characteristics

- Initial absorption is delayed for the first 10 hours after dosing
- The peak is a single peak 14 hours after dosing, followed by a gradual decline.



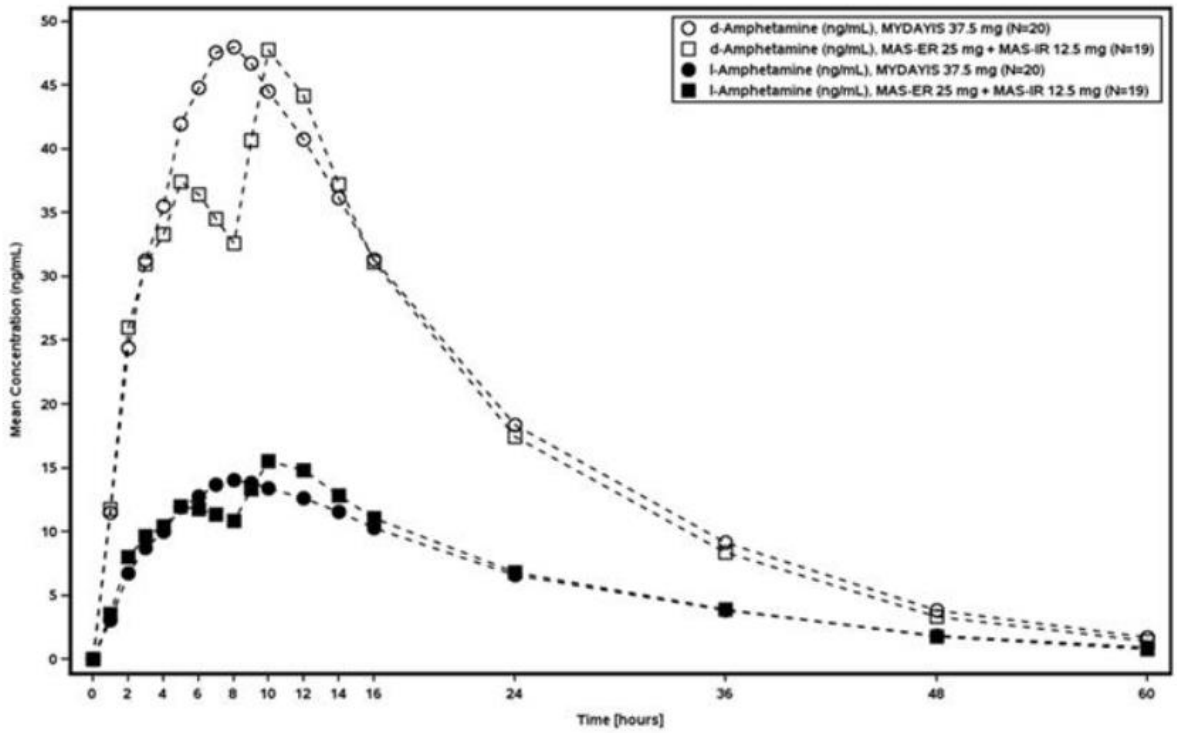
Mydayis (Mixed Salts of a Single-Entity Amphetamine Product)

Booster dose is NOT covered

Characteristics

- Comparable plasma concentration of mixed amphetamine salts ER followed by immediate release administered 8 hours later.
- Time to peak is 7 to 10 hours.
- Steady state is occurred between 7 to 8 days of dosing.
- **Total Duration:** 16 hours

Figure 1 Mean Plasma Concentrations of d- and l-amphetamine Following Oral Administration of MYDAYIS 37.5 mg vs MAS-ER 25 mg Followed by Immediate-Release MAS-IR 12.5 mg 8 Hours Later in Adults



Vyvanse / Vyvanse Chewable (lisexamfetamine)

Booster dose is NOT covered

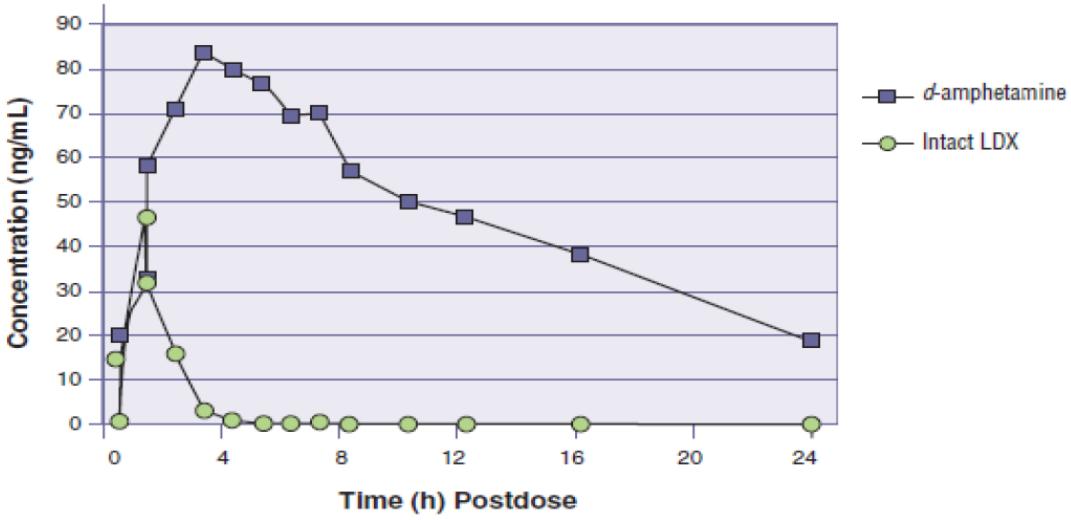
Characteristics

- Time to peak is 3.5 to 4.5 hours.
- Vyvanse is converted to active components by hydrolytic activity in the red blood cells. Substantial hydrolysis occurs even at low hematocrit levels. Vyvanse is not metabolized by cytochrome P450 enzymes.
- **Total Duration:** 10 hours

Special Considerations:

- Due to unique metabolism, Vyvanse exhibits low inter-patient variability. There is low potential for abuse as the extended release mechanism can not be circumvented by crushing, since it is a prodrug slowly activated in the blood stream.

Figure 1. Concentration-time profile of *d*-amphetamine and intact Vyvanse (LDX) following day 7 administration of Vyvanse 70 mg (Krishnan and Kehner 2006)



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Booster Dosing is Covered

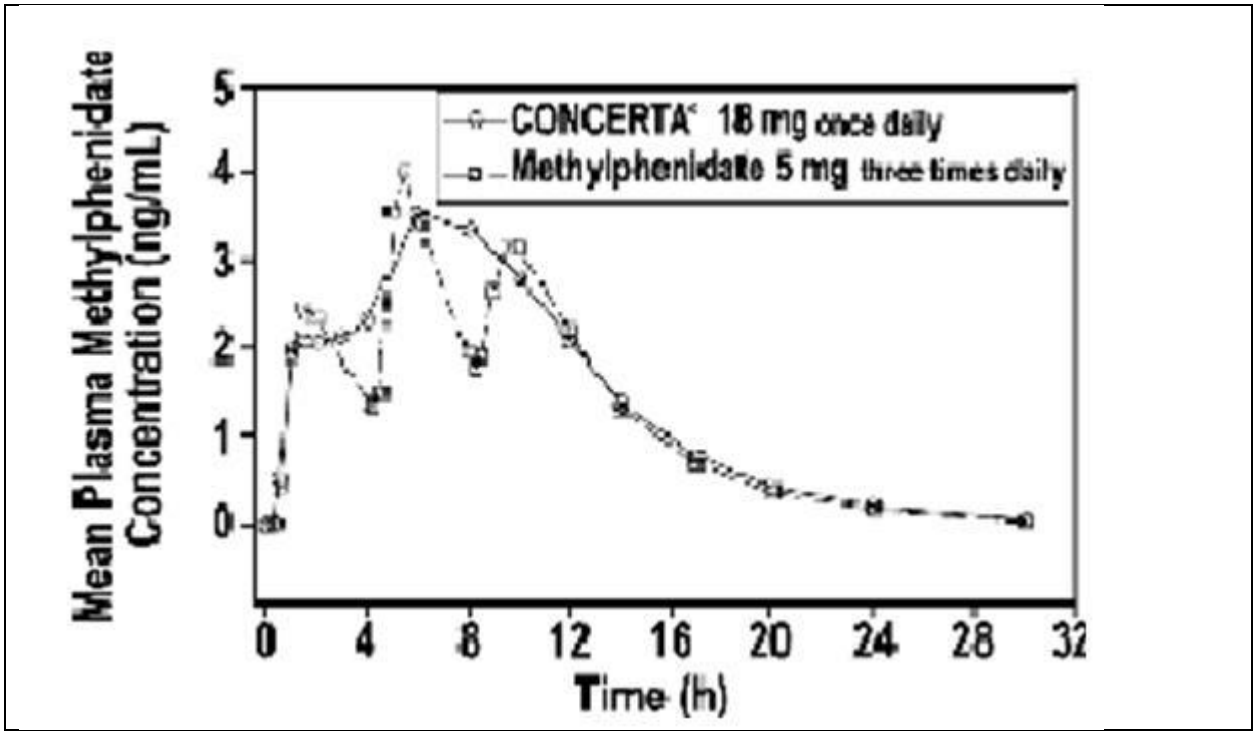
Concerta (Methylphenidate)

Booster dose is covered

- *Kinetics do not support this so continued coverage will be evaluated*

Characteristics

- Relative bioavailability of methylphenidate three times daily administered every 4 hours while minimizing the fluctuations between peak and trough concentrations.
- The peak is biphasic, with the first peak occurring 1 hour after dosing, followed by a gradual increase in concentration before reaching a second peak at 6 to 10 hours.
    - ~33% of active compound released in the morning
    - ~67% of active compound released in the afternoon
- **Total Duration:** 10 to 12 hours



Focalin XR (dexmethylphenidate)

Booster dose is covered

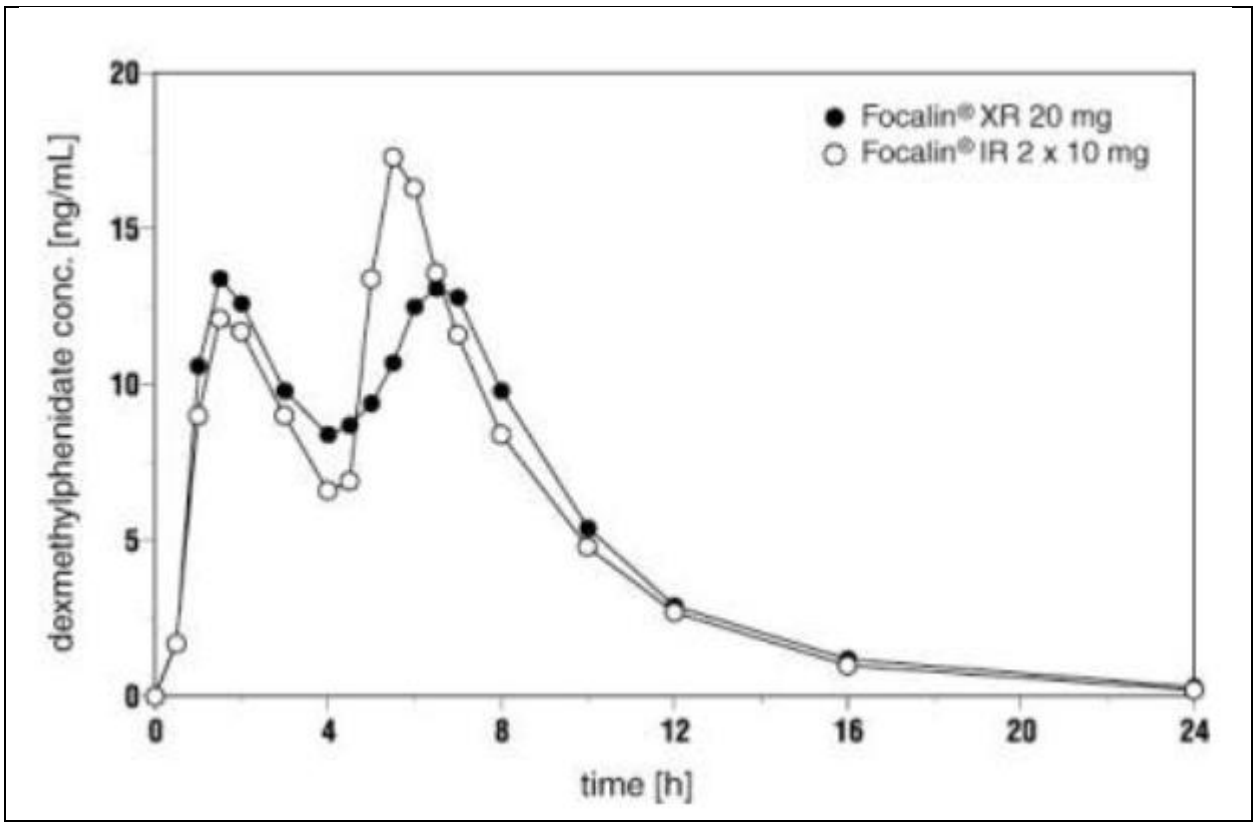
- *Kinetics do not support this so continued coverage will be evaluated*

Characteristics

- Has a relative bioavailability of dexmethylphenidate twice daily administered every 4 hours with less peak and trough fluctuations
- The peak is biphasic, with the first peak occurring 1 to 4 hours after dosing and a second peak 4.5 to 7 hours after dosing.
  - 50% immediate release[2]
  - 50% delayed release over 10 to 12 hours (bimodal)
- **Total Duration:** 12 hours

Special Consideration:

- Release is pH dependent and proton pump inhibitors may result in an excessive response shortly after administration and a diminished response at the end of the dosing interval.
- *Continued coverage concurrently with Proton Pump Inhibitors will be evaluated*



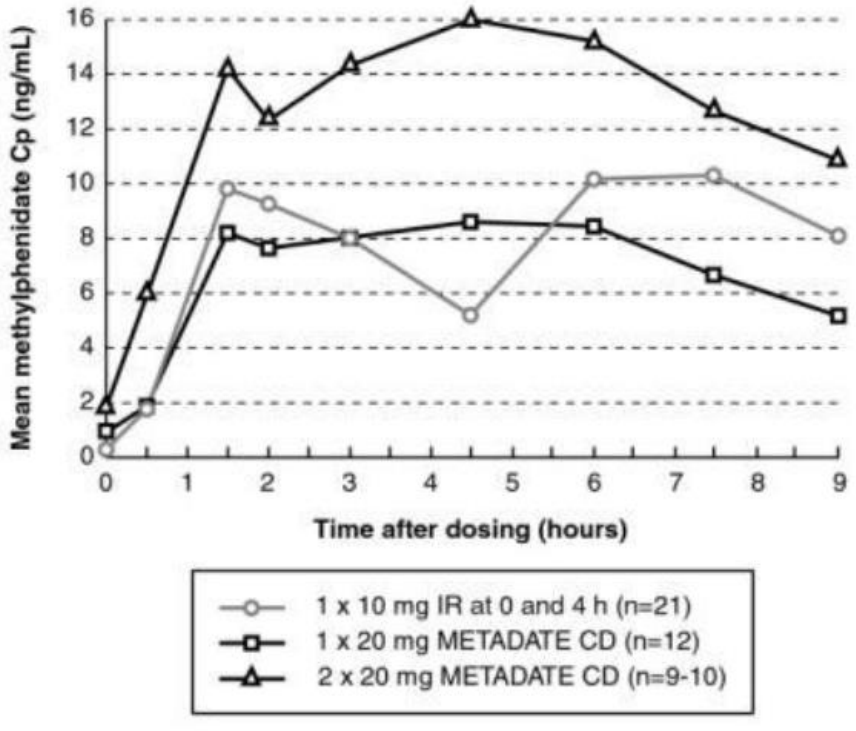
Methylphenidate CD

Booster dose is covered

Characteristics

- Has a relative bioavailability of methylphenidate twice daily administered every 4 hours with less peak and trough fluctuations
- The peak is biphasic, with the first peak occurring 1.5 hours after dosing and a second peak 4.5 hours after dosing.
  - 30% immediate release
  - 70% delayed release over 8 to 12 hours (bimodal)
- **Total Duration:** 8 to 12 hours

FIGURE 1
Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD



Ritalin LA (Methylphenidate)

Booster dose is covered

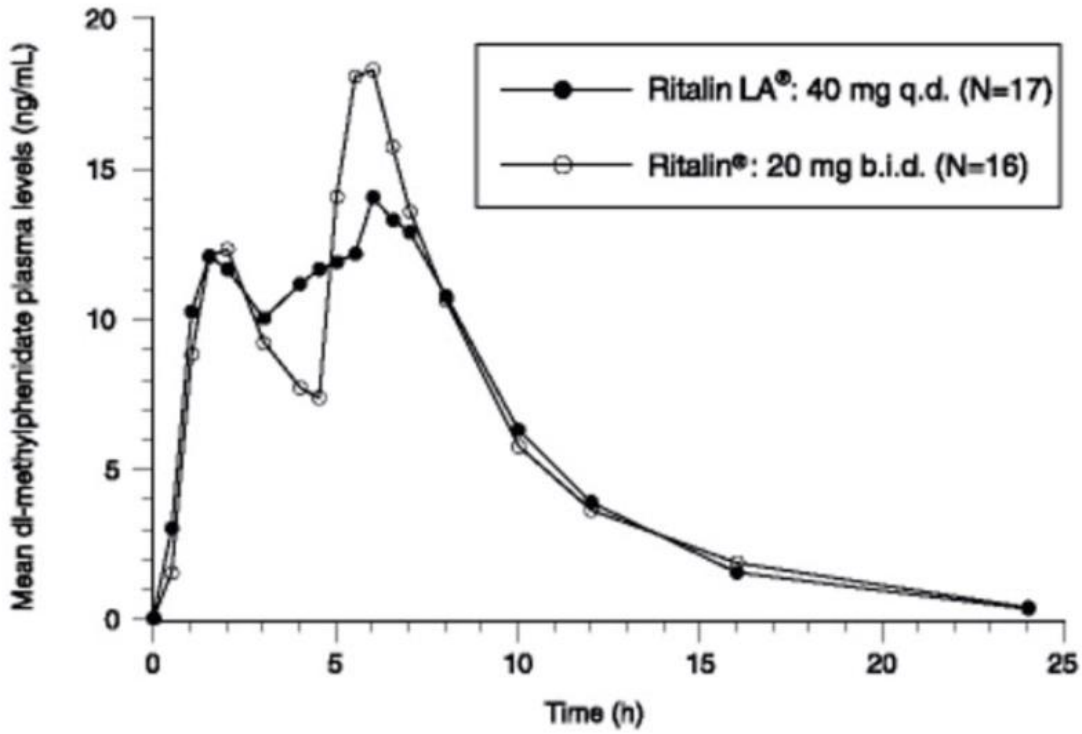
Characteristics

- Has a relative bioavailability of methylphenidate twice daily administered every 4 hours with less peak and trough fluctuations
- The peak is biphasic, with the first peak occurring 1 to 3 hours after dosing and a second peak 2 to 7 hours after dosing.
  - 50% immediate release
  - 50% delayed release over 8 to 12 hours (bimodal)
- **Total Duration:** 8 to 12 hours

Special Consideration:

- Release is pH dependent and proton pump inhibitors may result in an excessive response shortly after administration and a diminished response at the end of the dosing interval.
- *Continued coverage concurrently with Proton Pump Inhibitors will be evaluated*

Figure 1: Mean Plasma Concentration Time-profile of Methylphenidate After a Single Dose of Ritalin LA 40 mg and Ritalin 20 mg Given in Two Doses 4 Hours Apart



Quillivant XR / Quillichew ER (Methylphenidate)

Booster dose is covered

Characteristics

- Peak levels are reached at about 5 hours after dosing
- **Total Duration:** 12 hours

Figure 2. Mean Methylphenidate Plasma Concentration-Time Profiles After Administration of 40 mg QuilliChew ER or Methylphenidate Immediate-Release Chewable Tablets (IRCT, 2 Equal Doses of 20 mg, 6 Hours Apart) Under Fasted Conditions in Healthy Volunteers

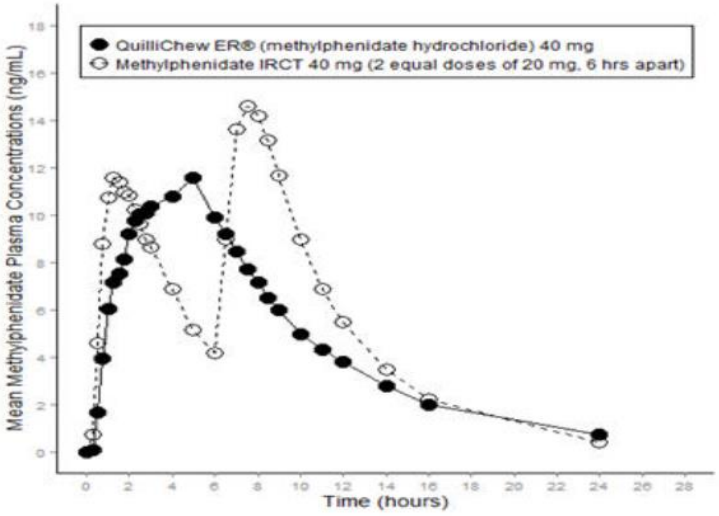
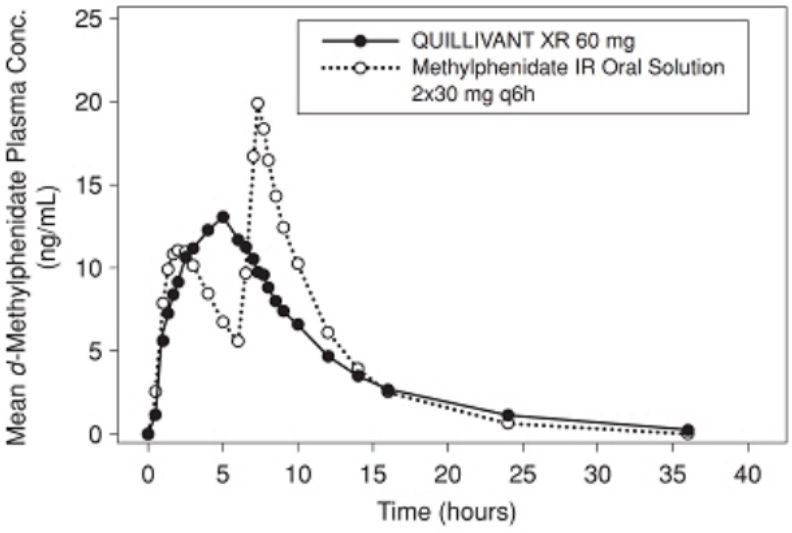


Figure 2. Mean *d*-Methylphenidate Plasma Concentration-Time Profiles



Resources

- Florida Center for Behavioral Health Improvements and Solutions (floridabhcenter.org)
- Treatment Strategies for Dosing the Second Generation Antipsychotics - Schwartz - 2011 - CNS Neuroscience & Therapeutics - Wiley Online Library
- Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis - The Lancet
- The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup (nih.gov)
- 2021.01 Newer Antipsychotics.pdf (utah.gov)
- https://autismguidelines.dmh.mo.gov/forClinicians.htm
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