050923 Uudet psykoosilääkkeet - lääke jolla on antipsykoottista tehoa

Yl juha kemppinen

050923 Uudet psykoosilääkkeet - lääke jolla on antipsykoottista tehoa

- Agenda:
- Yleistä lääkkeistä joilla on antipsykoottista vaikutusta

1) Asenapiini (Sycrest)
2) Lurasidoni (Latuda) - Suomessa
3) Brekspipratsoli (Rxulti)- Suomessa
4) Karipratsiini (Reagila) - Suomessa
5) Pimavanseriini (Nuplazid)
6) Iloperidoni (Fanaptum)
7) Lumateperoni (Caplypta)
8) Loksapiini (Loxapac, Loxitane)
9) Amisulpiridi (Solian)
10) Molindoni (Moban)
11) Muita uusia lääkkeitä joilla antipsykoottista tehoa

Yleistä lääkkeistä joilla on antipsykoottista vaikutusta

- yleistä tietoutta

050923 Psyykenlääkkeet (uudet) jolla on antipsykoottista vaikutusta

Taulukko 1. Esimerkkejä eri lääkeaineryhmien näytönasteesta ja vaikuttavuudesta eri häiriöissä Käypä hoito -suositusten mukaan. Näytön asteen luokittelu: A = vahva; B = kohtalainen; C =niukka; D = ei tutkimusnäyttöä.

NNT = number needed to treat.

Häiriö ja sen hoitotavoite	Lääkeaine tai lääkeaineryhmä	Näytön aste	NNT-luku
Skitsofrenia, relapsin ehkäisy	Toisen polven psykoosilääkkeet	A	5
Kaksisuuntainen tyypin 1 mielialahäiriö, ylläpitohoito	Toisen polven psykoosilääkkeet:		
	Ketiapiini ja olantsapiini	A	
	Aripipratsoli ja risperidoni (pitkävaikutteinen injektio)	B	
	Mielialan tasaajat:		
	Litium	A	
	Valproaatti	B	
	Lamotrigiini (vain masennusjaksojen ehkäisy)	A	
Masennustila, masennusjakson hoito		A	6
Toistuva masennus, ylläpitohoito		A	4
Epävakaa persoonallisuushäiriö, erityisesti impulsiivisuuden, vihamielisyyden ja tunnesäätelyoireiden hoito	Psykoosilääkkeet: haloperidoli, olantsapiini, ketiapiini ja aripipratsoli	B	
	Mielialan tasaajat: valproaatti, karbamatsepiini, lamotrigiini ja topiramaatti	C	

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Taulukko 2. Psyykenlääkehoidon suositeltu kesto akuuttivaiheessa ja ylläpitovaiheiessa eri häiriöryhmissä.

Häiriö	Akuuttihoidon kesto	Ylläpitohoidon kesto	Hoitosuositus
Skitsofrenia	Noin 6 viikkoa, positiivisten psykoosioireiden lievittymisen mukaan	2–5 vuotta ensimmäisen psykoosijakson jälkeen	Käypä hoito
Kaksisuuntainen mielialahäiriö, maniajakso	4 viikkoa oireiden lievittymisen jälkeen, noin 3–6 kuukautta	Tyypin 1 häiriössä elämänmittainen	Käypä hoito
Depressio	6 kuukautta oireettomuuden saavuttamisen jälkeen	Useita vuosia toistuvassa masennuksessa	Käypä hoito

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- Pitoisuusmittaukset
- Jäännöspitoisuuden mittaaminen
- Kun mitataan lääkeaineiden seerumipitoisuuksia, **näytteenotto ajoitetaan niin sanotun jäännöspitoisuuden ajankohtaan, joka on aamulla ennen aamulääkkeen ottoa**. Viitearvot ovat jäännöspitoisuuksia.
- Kun lääkkeen annostelua muutetaan, muutoksen jälkeinen pitoisuuden vakaa tila saavutetaan noin **5 puoliintumisajan** jälkeen.
- Siten esimerkiksi, jos **litiumin** (T½ 14–30 tuntia) annoksen noston jälkeen halutaan selvittää, minkä pitoisuuden uusi annos tuottaa, tulisi näyte ottaa vasta noin 1 viikon kuluttua annosmuutoksesta. **Tosin lähes 90 % pitoisuuden kasvusta tapahtuu jo 3 puoliintumisajan aikana**.
- Keskeiset mitattavat lääkeaineet
- Litiumin tai trisyklisten masennuslääkkeiden käyttö edellyttää **aina** seerumipitoisuuksien mittaamista tehokkaan ja turvallisen lääkeannoksen määrittämiseksi. Pitoisuusmittauksia tulee hyödyntää myös käytettäessä valproaattia tai karbamatsepiinia.
- Klotsapiinin kohdalla niiden käyttö on myös vahvasti suositeltavaa.
- Lähes kaikkien muiden psyykenlääkkeiden kohdalla pitoisuusmittauksista voi olla hyötyä tietyissä ongelmatilanteissa.

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- Psykoosilääkehoidossa **vaste ilmenee yleensä 2–6 viikossa**, mutta vaste tulee osalle potilaista jo tätä aiemmin. Tätä **ei kuitenkaan voi nopeuttaa käyttämällä lääkehoidossa tavanomaista suurempia annoksia**. Psykoosilääkkeitä vertailtaessa niiden annosten muuttaminen annosekvivalenteiksi helpottaa antipsykoottisen tehon vertailua (taulukko **1**).
- Psykoosilääkkeiden teho skitsofrenian hoidossa on osoitettu niin akuuttihoidossa kuin uusien sairausjaksojen estossa. Skitsofrenian hoidossa psykoosilääkehoito on keskeistä ja lääkehoidon tarve on pitkäaikainen. Sairauteen liittyy usein vaikeus hahmottaa sairauttaan, sen oireita ja hoidon tarvetta.
- **Kaikki psykoosilääkkeet vähentävät psykoosioireita jonkin verran jo ensimmäisten parin tunnin aikana**. Antipsykoottinen teho on osoitettavissa koko akuutin hoitojakson ajan.
- **Klotsapiini** on osoittautunut tehokkaimmaksi psykoosilääkkeeksi. Lääkkeiden välillä on vähän tehoeroja, mutta haittavaikutuksissa on merkittäviä eroja ja yksilöllistä vaihtelua.

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- **Akuutin vaiheen jälkeen psykoosilääkkeet suojaavat tehokkaasti uudelta psykoosijaksolta**. Vuodet 1959–2017 kattavassa meta-analyysissa, jossa tarkasteltiin 75 lumekontrolloidun tutkimuksen tuloksia 7–12 kuukauden seurannan aikana lähes 10 000 potilaalla, relapsin todennäköisyys psykoosilääkkeen aikana oli 24 % ja lumelääkkeen aikana 61 %. Lääkehoidon merkittävä hyöty näkyy myös potilaan paremmassa toimintakyvyssä ja elämänlaadussa.
- Jos seurataan vain ensipsykoosiin sairastuneita 1–2 vuotta remission jälkeen, vaara sairastua uudelleen on lääkehoidon aikana 19 % ja lääkehoidotta olleilla tai sen asteittain lopettaneilla 53 %. Psykoosilääkehoidon lopettaneiden huonompi ennuste alkaa näkyä 2 kuukauden jälkeen. **Ilman psykoosilääkehoitoa noin puolet psykoosipotilaista sairastuu uudelleen 1 vuoden kuluessa. Ylläpitolääkehoidon suojavaikutuksen on osoitettu pysyvän ainakin 2 vuoden ajan.**
- Uudelleen sairastumiseen vaikuttaa psykoosialttiuden lisäksi myös oleellisesti potilaan sitoutuminen omaan hoitoonsa. Erityisen merkittävää ennusteen kannalta on, jatkaako potilas vaikuttavaksi havaittua lääkehoitoaan. Suomessa klotsapiinin käytön yhteydessä ennuste on keskimääräistä parempi.

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- **Pitkävaikutteinen injektiolääkehoito** on tehokas lisäsuoja uutta psykoosijaksoa vastaan. Kaikki käytössä olevat pitkävaikutteiset psykoosilääkkeet ovat tehokkaita. Hoitomyöntyvyys niille on myös hyvä. **Psykoosioireettomien eli remissiossa olevista potilaista pitkävaikutteisen psykoosilääkehoidon aikana keskimäärin 15 potilasta sadasta sairastuu uudelleen 1 vuoden kuluessa**. Sairastumisriski on **kaksinkertainen** niillä, jotka eivät saavuta akuuttihoidossa täyttä oireremissiota. **Lääkehoitonsa keskeyttäneillä relapsin vaara on 1 vuoden kuluessa yli 50 %.**
- Hoitomyöntyvyys on hoidon toteuttamisessa keskeinen asia, minkä takia on tärkeää valita potilaalle paitsi tehokas myös mahdollisimman hyväksyttävä lääke. Usein hoitomyöntyvyys paranee, jos lääkehoito voidaan toteuttaa käyttämällä pitkävaikutteista injektiota. Pitkävaikutteisten injektiolääkkeiden annosvälit vaihtelevat valmisteittain 2 viikosta jopa 3 kuukauteen. Joistakin valmisteista on käytettävissä myös suussa hajoavia tabletteja, oraaliliuoksia ja akuuttihoitoon tarkoitettuja lyhytvaikutteisia injektioita.

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- Psykoosilääkkeiden käyttö on **vuosia kestävää** pitkäaikaiskäyttöä sen jälkeen, kun riittävä vaste on saavutettu pienimmällä tehokkaalla annoksella ja siedettävillä haittavaikutuksilla. Potilaalla voi olla pyrkimys liian aikaiseen tai nopeaan lääkeannoksen vähentämiseen tai lääkehoidon lopettamiseen. Potilasta kannattaa tällöin ohjata ja opastaa lääkehoitonsa mahdollisimman hyvään hallintaan. Lääkemuutokset tulisi tehdä aina yhteisymmärryksessä ja hyvässä yhteistyössä hoitavan lääkärin kanssa.
- **Lääkeannoksen pienentämisessä tulisi olla erittäin varovainen**. Keskeinen syy tähän on se, että lääkehoidossa on tärkeää varmistaa keskushermoston adaptoituminen muutokseen, josta seuraa sopeutumisreaktioita useissa eri välittäjäainejärjestelmissä (taulukko **2**).
- **Annoksen pienentäminen (5–10 % kerrallaan) pitäisi toteuttaa asteittain 3–6 kuukauden välein tapahtuvilla muutoksilla**. T
- oteuttaminen edellyttää potilaan tilan tarkkaa seuraamista vieroitushaittavaikutusten varalta. Hallittu muutos etenee vähittäin pienenevin muutoksin ja kestää 2–3 vuotta.

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5 x T ½ = steady state

Box 1.1 Why Five Half-Lives Equates to Steady State

Example: Antipsychotic with a 24-hour half-life is dosed once daily. The accumulated medication levels and contribution from each dose are noted below. After five half-lives, the medication is at 97% of the steady state value.

	1st dose	2nd dose	3rd dose	4th dose	5th dose	Total
24 hours	50%	–	–	–	–	50%
48 hours	25%	50%	–	–	–	75%
72 hours	12.5%	25%	50%	–	–	87.5%
96 hours	6.25%	12.5%	25%	50%	–	93.75%
120 hours	3.125%	6.25%	12.5%	25%	50%	96.875%

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5 x T ½ = steady state

Table P3 Mean half-life of commonly used oral antipsychotics and important metabolites [8–18, 3, 19, 20]

Drug	$T_{1/2}$ (hours)
First-generation antipsychotics	
Chlorpromazine	11.05–15
Fluphenazine	13
Haloperidol	24
Loxapine	4
7-OH loxapine	??[a]
Molindone	2[b]

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5 x T ½ = steady state

Drug		$T_{1/2}$ (hours)
Perphenazine	**Peratsin**	9–12
Zuclopenthixol	**Cisordinol**	17.6
Newer antipsychotics		
Amisulpride	**Solian**	12
Aripiprazole	**Abilify**	75
Asenapine sublingual	**Sycrest**	24
Asenapine transdermal patch		30[c]
Brexpiprazole	**Rxulti**	91
Cariprazine	**Reagila**	31.6–68.4
Desmethylcariprazine (DCAR)		29.7–39.5 (DCAR)
Didesmethylcariprazine (DDCAR)		314–446 (DDCAR)
Clozapine	**Leponex**	9–17
Norclozapine		20
Iloperidone	**Fanaptum**	15–22
Lumateperone	**Caplypta**	18
Lurasidone	**Latuda**	28.8–37.4[d]
Olanzapine	**Zyprexa**	30
Paliperidone (9-OH risperidone)[e]	**Xeplion**	23
Quetiapine	**Ketipinor**	7
Norquetiapine		12
Risperidone	**Risperdal**	3
Paliperidone (9-OH risperidone)[f]		21
Sertindole	**Serdolect**	60–73
Ziprasidone	**Ziprasidon**	7

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Comment

Half-lives may be markedly prolonged in individuals receiving metabolic inhibitors or who have lower-functioning polymorphisms of cytochrome P450 enzymes, other relevant enzymes, or transporters involved in drug disposition. Conversely, half-lives may be significantly shorter than the mean in individuals exposed to inducers, or who have higher-functioning polymorphisms of cytochrome P450 enzymes, other relevant enzymes, or transporters involved in drug disposition.

[a] Based on studies of inhaled loxapine, the half-life of 7-OH loxapine is likely to be substantially longer [21].
[b] The therapeutic effects persist for 24–36 hours despite the absence of active metabolites [18].
[c] After patch removal.
[d] Repeated dosing in adult schizophrenia patients. Single dose half-life in volunteers is 18 hours [22].
[e] When administered as oral paliperidone.
[f] When derived from orally administered risperidone.

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Table P1 Oral dose equivalency of commonly used first- and second-generation antipsychotics in acute schizophrenia [1, 2]

Medication	Oral equivalent (mg)
First generation	
Haloperidol	1.00
Fluphenazine	1.25
Trifluoperazine	2.50
Perphenazine	3.75
Thiothixene	3.75
Zuclopenthixol	3.75
Loxapine	12.5
Chlorpromazine	37.5
Second generation	
Amisulpride	82.4
Aripiprazole	1.82
Brexpiprazole	0.53
Cariprazine	1.21
Lurasidone	23.2
Risperidone	1.00
Olanzapine	2.15
Ziprasidone	29.5

Table P2 Antipsychotic nmol/l to ng/ml unit conversion

Antipsychotic	To obtain plasma levels in ng/ml divide levels in nmol/l by the value below:
Amisulpride	2.71
Aripiprazole	2.23
Asenapine	3.50
Brexpiprazole	2.31
Cariprazine	2.34
Chlorpromazine	3.14
Clozapine	3.06
Flupenthixol	2.30
Fluphenazine	2.29
Haloperidol	2.66
Loxapine	3.05
Lurasidone	2.03
Olanzapine	3.20
Paliperidone	2.34
Perphenazine	2.48
Risperidone	2.44
Thiothixene	2.25
Trifluoperazine	2.45
Zuclopenthixol	2.49

Ekvalentit annokset

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Maksa

Table 3.2 Child–Pugh criteria scoring and interpretation [44]

Measure	1 point	2 points	3 points
Total bilirubin (mg/dl)	< 2.0	2.0–3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8–3.5	< 2.8
INR*	< 1.70	1.71–2.30	> 2.30
Ascites	None	Mild	Moderate/Severe
Hepatic encephalopathy	None	Grade I–II (suppressed with meds)	Grade III–IV (or refractory)

Points	Class	1-year survival	2-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

* International normalized ratio (INR): this calculation reflects the ratio of a patient's prothrombin time to a control sample, normalized for that manufacturer's equipment and assay

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Munuainen

Table 3.3 Staging of kidney disease [51]

Stage	eGFR (ml/min*)
1. Normal	≥ 90
2. Mild	60–89
3a. Moderate	45–59
3b. Moderate	30–44
4. Severe	15–29
5. Failure	< 15

* This is based on the average body surface area of 1.73 m^2. Individuals with eGFR < 60 ml/min/1.73 m^2 for 3 months are classified as having chronic kidney disease.

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050923 Psyykenlääkkeet (uudet) jolla on antipsykoottista vaikutusta

Taulukko 1. Eräiden psykoosilääkkeiden **95 % tehosta tuottava vuorokausiannos (ED95%)** ja siitä laskettu ekvivalenttiannos, joka vastaa 1 mg:n suun kautta otetun risperidonin tehoa.

[1] ED95% (keskiluku) on vuorokausiannos (*per os*), jolla saavutetaan 95 % lääkkeen antipsykoottisesta tehosta.
[2] Lääkeannos, joka vastaa suun kautta annosteltavan 1 mg risperidoniannoksen antipsykoottista tehoa.

Lääke	ED95%[1]	Ekvivalenttiannos[2] (vastaa **1 mg risperidonia per os)**
Amisulpridi	537,0 mg	85,8 mg
Aripipratsoli	11,5 mg	1,8 mg
Asenapiini	15,0 mg	2,4 mg
Brekspipratsoli	3,36 mg	**0,54** mg
Haloperidoli	6,3 mg	1,01 mg
Ketiapiini	482,0 mg	77,0 mg
Lurasidoni	147,0 mg	**23,5** mg
Olantsapiini	15,2 mg	2,4 mg
Paliperidoni	13,4 mg	2,1 mg
Risperidoni	6,3 mg	1,0 mg
Sertindoli	22,5 mg	3,6 mg
Tsiprasidoni	186,0 mg	30,0 mg

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Taulukko 3. Psykoosilääkkeiden ja mielialaa tasaavien lääkkeiden metabolia.

ABC = ATP-binding cassette; AKR = aldo-keto-reduktaasi; BCRP = breast cancer resistance protein; CR = karbonyylireduktaasi; CYP = sytokromi P-450; P-gp = P-glykoproteiini; UGT = UDP-glukuronosyyiltransferaasi.

Amisulpiridi	yli 90 % erittyy munuaisten kautta
Aripipratsoli	CYP2D6, CYP3A4, P-gp
Asenapiini	CYP1A2, UGT1A4
Brekspipratsoli	CYP3A4, CYP2D6
Haloperidoli	CYP2D6, CYP3A4, AKR, UGT, P-gp
Karbamatsepiini	CYP1A2, CYP2C8, CYP3A4, epoksidihydrolaasi, UGT2B7, BCRP, P-gp
Karipratsiini	CYP2D6, CYP3A4
Ketiapiini	CYP3A4, CYP2D6, P-gp (ABCB1)
Klooripromatsiini	CYP1A2, CYP2D6, P-gp

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Klooriprotikseeni	CYP2D6 (?), CYP3A4
Klotsapiini	CYP1A2, CYP2C19, CYP3A4, P-gp
Lamotrigiini	UGT1A4, UGT3B7, P-gp, BCRP
Levomepromatsiini	CYP3A
Litium	erittyy munuaisten kautta virtsaan
Loksapiini	CYP3A4, CYP2D6, CYP1A2, CYP2C8, CYP2C19, FMO
Lurasidoni	CYP3A4
Olantsapiini	UGT1A4, CYP1A2, UGT2B10, FMO, CYP2D6, P-gp (ABCB1)
Okskarbatsepiini	AKR, UGT2B15, P-gp (ABCB1)

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Taulukko 3. Psykoosilääkkeiden ja mielialaa tasaavien lääkkeiden metabolia.

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Paliperidoni	60 % erittyy munuaisten kautta, CYP3A4, UGT, P-gp (ABCB1), BCRP (ABCG2)
Perfenatsiini	CYP2D6, CYP1A2, CYP2C19, CYP3A4
Promatsiini	CYP1A2, CYP2A6, CYP2C19, CYP3A4
Risperidoni	CYP2D6, CYP3A4, P-gp (ABCB1), BCRP (ABCG2)
Sertindoli	CYP2D6, CYP3A4
Sulpiridi	erittyy munuaisten kautta, P-gp (ABCB1)
Tioridatsiini	CYP1A2, CYP2D6, CYP3A4
Valproiinihappo	UGT1A3, UGT1A6, UGT2B7, CYP2A6, CYP2B6, CYP2C9, CYP219, beetaoksidaatio
Tsiprasidoni	CYP3A4, aldehydioksidaasi

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

1. Asenapiini (Sycrest)

1. Asenapiini (Sycrest)

Sublinguaalinen, >99% ensivaiheen metabolia
Transdermal patch (1x pv) → matala riski lääkeinteraktioihin
Metallinmaku

ASENAPINE (Saphris, Secuado) Fact Sheet

Bottom Line:
Since there are no clear advantages over other atypical antipsychotics, the only reason to prescribe Saphris or Secuado is if your patient can't or doesn't want to swallow a pill. Mouth numbness (Secuado), sedation, dizziness, akathisia, weight gain, and potential for allergic reaction are significant liabilities. Not recommended for first-line use.

FDA Indications:
Schizophrenia; bipolar disorder, acute and maintenance treatment of manic or mixed episodes (adults, children 10–17 years).

Off-Label Uses:
Bipolar maintenance; bipolar depression; behavioral disturbances; impulse control disorders.

Dosage Forms:
- **SL tablets:** 2.5 mg, 5 mg, 10 mg. (Must be taken sublingually because if swallowed, too much medication is metabolized by the liver during first-pass metabolism.)
- **Transdermal patch:** 3.8 mg, 5.7 mg, 7.6 mg/24 hour patch.

Dosage Guidance:
- Schizophrenia: Start 5 mg BID, and increase as needed up to 10 mg BID.
- Bipolar (adults): Same dosing as schizophrenia.
- Bipolar (children): Start 2.5 mg BID, increase as needed up to 10 mg BID.
- Do not swallow tablets. Avoid food or drink for 10 minutes after taking (they significantly reduce absorption and bioavailability).
- For patch: Start 3.8 mg/24 hours, increase as needed to 5.7 mg/24 hours or 7.6 mg/24 hours after one week. Patch should be applied to hip, abdomen, upper arm or upper back area.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Antipsychotics

Puzantian T and Carlat D, 2020

1. Asenapiini (Sycrest)

Ei maksaongelmaisille, 7x pitoisuus!

Side Effects:

- Most common: Akathisia (seems to be dose-related), oral hypoesthesia (numbing of the tongue or decreased oral sensitivity), somnolence, dizziness, extrapyramidal symptoms, weight gain.
- Serious but rare: Hypersensitivity reactions including anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, or rash; orthostatic hypotension and syncope, particularly early in treatment (FDA warning, 9/2011).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT2A receptor antagonist.
- Metabolized by glucuronidation and CYP1A2; t ½: 24 hours. Inhibitor of 2D6; may double paroxetine levels. Smoking may induce metabolism and may lower levels of asenapine via 1A2 induction; adjust dosing. CYP1A2 inhibitors (eg, fluvoxamine) may increase levels of asenapine; adjust dose.
- Caution with antihypertensive agents and other drugs that can cause additive hypotension or bradycardia.

Clinical Pearls:

- Has a receptor-binding profile similar to clozapine, although asenapine has very little anticholinergic activity.
- Weight gain seems to be a problem in many patients.
- Contraindicated in patients with severe hepatic impairment due to 7-fold higher levels.
- Most useful for patients who don't like swallowing pills.

Fun Fact:

Black cherry flavor developed after patients complained about original tablets.

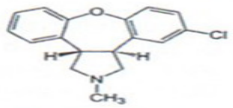
Puzantian T and Carlat D, 2020

1. Asenapiini (Sycrest)

BID bis i die = 2x pvssä
5mg kahdesti päivässä aloitus, 10mg tavoite

Cafer, 2020

2009
$599–$728



Asenapine (SAPHRIS)

a SEN a peen / SAFF ris
"Sapphire (for an) Ass in a pine"

- Antipsychotic (SGA)
- D2 antagonist - ⇩ DA
- 5-HT_{2A} antagonist - ⇩ DA
- Alpha-adrenergic antagonist

2.5
5
10
mg

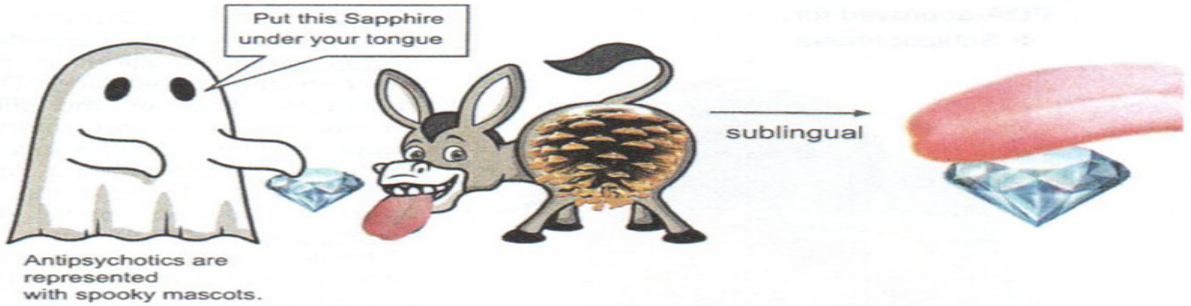
FDA-approved for:
- Schizophrenia
- Bipolar disorder (ages 10+)
  - acute manic/mixed episode
  - maintenance

Used off-label for:
- Acute agitation

Asenapine (Saphris), approved in 2009, is the only sublingual antipsychotic. The patient should not eat or drink for 10 minutes after taking it because serum levels will be decreased by about 15%. The swallowed portion of the medication is subject to first-pass metabolism in the liver before entering the general circulation. Some patients report lingering bad taste or numbing of the tongue. Patients complained about the original taste, so it now has a black cherry flavor. The patent for Saphris expires in 2021.

Asenapine can be used as a rapid-acting PRN for acute agitation. With sublingual administration it is absorbed directly into the bloodstream. Peak serum concentration is reached within 1 hour. The label recommends BID dosing, but half-life is 24 hours, so dosing it once daily at HS is a viable treatment option.

Asenapine is approved for schizophrenia and bipolar disorder. It is not a first-line choice for either condition due to cost, and rare idiopathic hypersensitivity reactions including anaphylaxis. Reactions may occur with the first dose.



Antipsychotics are represented with spooky mascots.

Other side effects may include sedation, hypotension, and dose-related akathisia. Asenapine has little potential for causing weight gain. Oral ulcers are possible. Anticholinergic effects are minimal. It is contraindicated with severe hepatic insufficiency, because levels may increase 7-fold.

Dosing: The "minimal effective" daily dose for psychosis is 10 mg. The label recommends starting 5 mg BID, but to minimize sedation it is best given at night only (half-life is 24 hours). 10 mg HS is also a reasonable starting dose and target dose. Maximum dose is 20 mg/day. The 2.5 mg dose is for ages 10–17. Avoid rapid discontinuation. Taper over 2–4 weeks.

Saphris is a fluffy, white tablet that is too delicate for bottling, so it comes in a special case containing 10 tabs.

Dynamic interactions:
- Antidopaminergic (moderate)
- EPS (dose dependent)
- Sedation (mild)
- Hypotensive effects
- Prolactin elevation (strong)
- Hyperglycemia (moderate)
- Weight gain (moderate)
- QT prolongation (low/moderate)

Kinetic interactions:
- 1A2 substrate (major)
  - Smoking inDuces 1A2 and may lower levels of asenapine
  - 1A2 inHibitors increase levels of asenapine, and dose adjustment is recommended.

page 10

1A2 substrate (minor)

SGAs

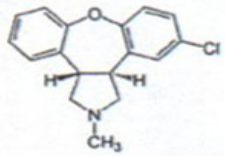
13

1. Asenapiini (Sycrest)

Laastari

Cafer, 2020

2019
$1,192



Asenapine transdermal (SECUADO)

a SEN a peen / seh kue AH doe

"See (the) caudal (end of an) Ass"

- Antipsychotic (SGA)
- D2 antagonist - ⇩ DA
- 5-HT_{2A} antagonist - ⇩ DA
- Alpha-adrenergic antagonist

3.8
5.7
7.6
/24 hr

FDA-approved for:

- Schizophrenia

Secuado (asenapine) is a once daily "transdermal drug delivery system" approved in 2019 for schizophrenia. This is the only transdermal antipsychotic. The transdermal route bypasses "first-pass" metabolism through the liver that oral medications are subject to. Asenapine tablets are not subject to "first-pass" metabolism either, because they are administered sublingually.

Onset of effect is much more gradual than with sublingual asenapine. It takes 12–24 hours for serum levels to peak (versus 1 hour sublingually).

Side effects include skin irritation (15%) and those associated with sublingual asenapine. Avoid exposing the patch to external heat sources during wear because drug absorption will be increased.

There have been no head-to-head comparisons between sublingual Saphris and transdermal Secuado.

Dosing: Start with the 3.8 mg/24 hours patch; The dosage may be increased to 5.7 mg/24 hours or 7.6 mg/24 hours, if needed, after one week; In short-term trials, there were more side effects and no added benefit with the maximum dose of 7.6 mg/24 hours

Dose equivalents: 3.8 mg/24 hours patch = 5 mg BID of sublingual asenapine; 7.6 mg/24 hours = 10 mg twice daily.

transdermal patch

Cafer's Psychopharmacology | cafermed.com

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1. Asenapiini (Sycrest)

Maksakokeet, K , Mg, EKG

Jacobson, 2023

Asenapine

Screening laboratory tests	• CMP (LFTs, potassium) and magnesium. Drug is contraindicated in severe hepatic impairment (Child-Pugh Class C). • Consider ECG for baseline QTc measurement, although the risk is lower with this drug compared to others in its class. Hypokalemia and hypomagnesemia magnify effects of QTc prolongation. • Consider pregnancy testing for patients of childbearing potential.
Monitoring laboratory tests	Routine laboratory testing is not required.

American Society of Health-System Pharmacists: AHFS Drug Information. Bethesda, MD, American Society of Health-System Pharmacists, 2016

U.S. National Library of Medicine: Asenapine: asenapine maleate tablet. DailyMed, July 8, 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f5cd9abb-40e3-4cb5-a1b2-40cdba8a1c7e. Accessed April 2022.

1. Asenapiini (Sycrest)

Meyer and Stahl, 2021

Asenapine (sublingual)	US FDA approval: Aug. 13, 2009 $T_{1/2}$ 24 hours Absolute oral bioavailability (with sublingual administration): 32%–40% after 10 minutes of buccal residence time. If water is given before 10 minutes, lower absorption is seen (see Figures 17.6 and 17.7) [9] T_{max} 1 hour Metabolism: Primarily CYP 1A2 and direct glucuronidation by the phase 2 enzyme UGT 1A4. CYP 3A4 and CYP 2D6 are minor pathways **Formulations:** Oral dissolving tablets	The strong CYP 1A2 inhibitor fluvoxamine at a dose of 25 mg BID had limited impact on drug levels, but a greater effect from higher fluvoxamine doses is possible. The asenapine dose may need to be adjusted in those circumstances [10] There is no impact from the strong CYP 2D6 inhibitor paroxetine, or the UGT 1A4 inhibitor valproate. Of note, asenapine increases paroxetine exposure two-fold, so paroxetine doses should be decreased by 50% [10]	There is no impact from the strong CYP 3A4 inducer carbamazepine [1]

1. Asenapiini (Sycrest)

Stahl, 5th ed, 2021

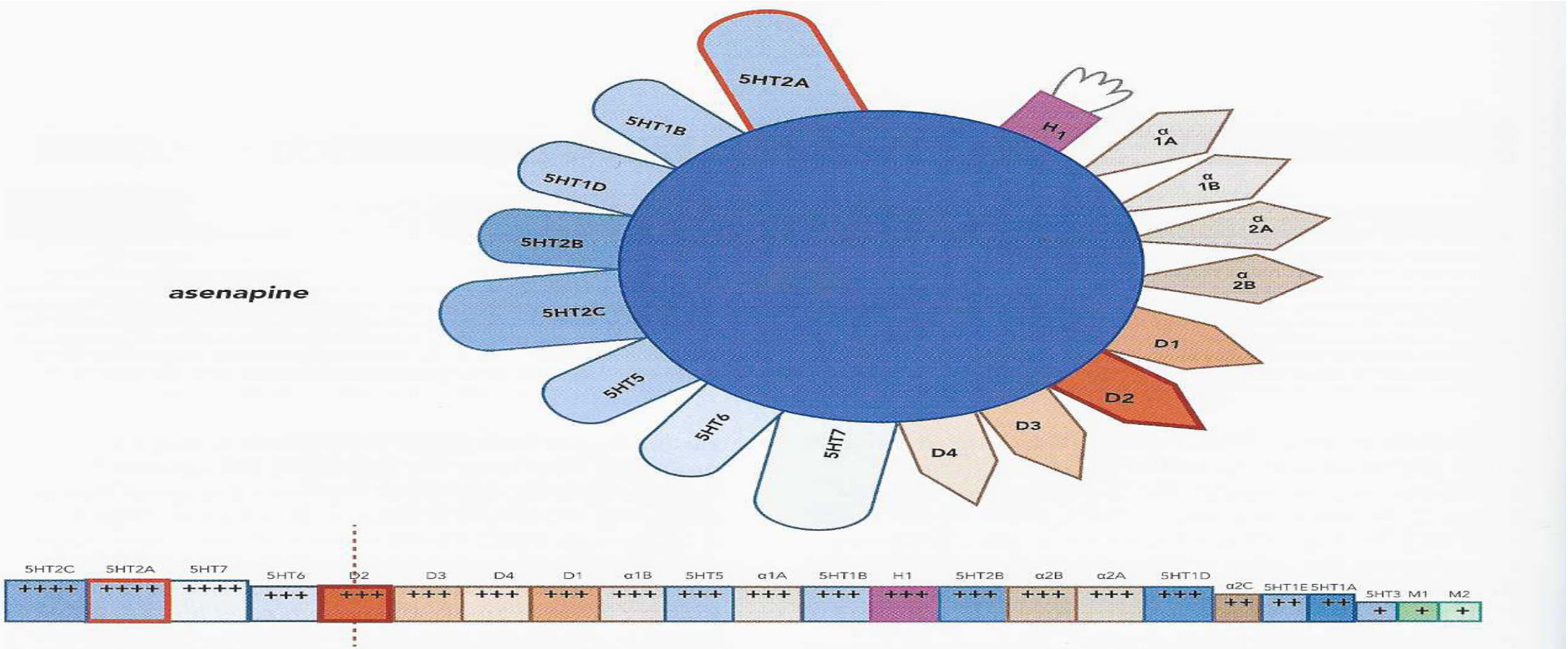


Figure 5-47 **Asenapine's pharmacological and binding profile.** This figure portrays a qualitative consensus of current thinking about the binding properties of asenapine. Asenapine has a complex binding profile, with potent binding at multiple serotonergic and dopaminergic receptors, α_1 and α_2 receptors, and H_1 histamine receptors. In particular, $5HT_{2C}$ antagonist properties may contribute to its efficacy for mood and cognitive symptoms, while $5HT_7$ antagonist properties may contribute to its efficacy for mood, cognitive, and sleep symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

2.Lurasidoni (Latuda)

2.Lurasidoni (Latuda)

QD=Kerran päivässä, ei titrausta, ei QTc riskiä
Ruuan kanssa, sivuvaikutukset: väsyttää, akatitisia, EPS
Ei painonnousua

LURASIDONE (Latuda) Fact Sheet

Bottom Line:
This drug offers some advantages, including no need for titration, once-daily dosing, relatively low-moderate metabolic profile, and relatively low QTc prolongation risk. However, its use is limited by the need to administer with ≥350 calories of food, potential for drug interactions, and side effects including sedation, akathisia, and EPS. In clinical practice, you might lump lurasidone with the other atypicals that cause little weight gain, such as aripiprazole and ziprasidone.

FDA Indications:
Schizophrenia (adults, adolescents 13–17); **bipolar depression** (as monotherapy and adjunct; adults, children 10–17).

Off-Label Uses:
Mixed depression; treatment-resistant depression; manic episodes; impulse control disorders.

Dosage Forms:
Tablets: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg.

Dosage Guidance:
- Schizophrenia (adolescents and adults): Start 40 mg QD, with food (at least 350 calories); no titration required. Usual dose 40 mg–160 mg/day. Max dose 160 mg QD (80 mg/day for adolescents).
- Bipolar depression (adults and children): Start 20 mg QD, with food (at least 350 calories); no titration required. Usual dose 20 mg–120 mg/day (20 mg–40 mg/day in kids). Max dose 120 mg QD (80 mg/day in kids), although doses >80 mg/day rarely more effective.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Puzantian T and Carlat D, 2020

2.Lurasidoni (Latuda)

T ½ = 18 h-40 h → noin 5-10 pv steady state

Side Effects:

- Most common: Sedation (dose-related), akathisia (dose-related), nausea, parkinsonism, agitation.
- Serious but rare: Orthostatic hypotension and syncope reported (rarely).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT2A and 5-HT7 antagonist; serotonin 5-HT1A partial agonist.
- Metabolized primarily through CYP450 3A4; t ½: 18 hours.
- Avoid use with medications that cause orthostasis, potent 3A4 inhibitors (eg, ketoconazole, clarithromycin), or inducers (eg, rifampin, St. John's wort, carbamazepine). Exercise caution/monitor when using in combination with moderate 3A4 inhibitors (eg, diltiazem); decrease lurasidone dose by 50% in patients taking moderate 3A4 inhibitors.

Clinical Pearls:

- Administration with food (at least 350 calories) increases bioavailability 2-fold and peak serum levels roughly 3-fold; fat content of meal is not important.
- Appears to be relatively weight-neutral and cardiometabolic parameters little affected in company-sponsored trials, although post-marketing observations have been limited. In kids, weight gain was a common side effect in studies.
- While lurasidone's efficacy in bipolar mania (in kids or adults) has not been established, it is approved for bipolar depression both in adults and kids.

Fun Fact:

One unique feature of Latuda is its high affinity for the 5-HT7 receptor, which has been linked to depression, learning/memory, cognition, anxiety, and pain. Unfortunately, to date, Latuda has shown no clear benefit over other atypical antipsychotics on these measures.

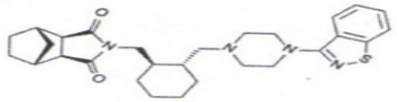
Puzantian T and Carlat D, 2020

2.Lurasidoni (Latuda)

Ei painonnousua (ja eniten lopetetaan!) , Hb1AC paranee?, EPS, CYP3A4

Cafer, 2020

#227
2010
$1,212–$1,490



Lurasidone (LATUDA)

loo RAS i dohn / la TUDE a
"Lured (to the) Latitude"

- Antipsychotic (SGA)
- D2 antagonist - ⇩ DA
- 5-HT_{2A} antagonist - ⇧ DA

20
40
60
80
120
mg

FDA-approved for:

- Schizophrenia
- Bipolar I depressive episode - monotherapy
- Bipolar depression as adjunct to lithium or valproate (Depakote, Depakene)—but contraindicated with carbamazepine (Tegretol)

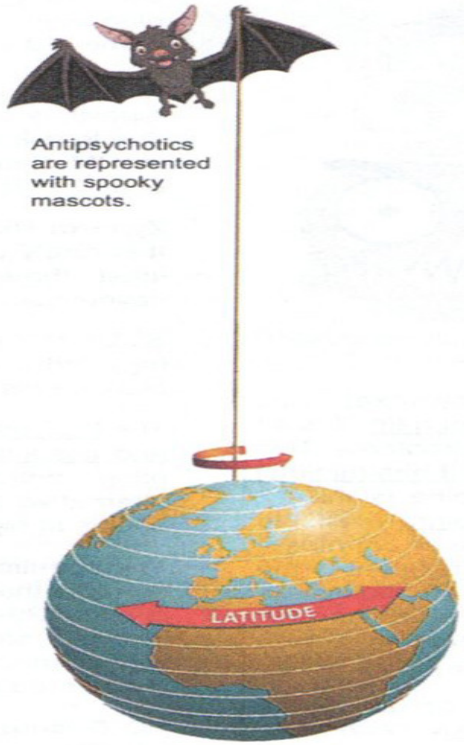
Used off-label for:

- Bipolar maintenance

Among antipsychotics, lurasidone (Latuda) is the most metabolically favorable. Weight loss is more likely than weight gain, and lurasidone actually *improves* Hgb A1c! The same can be said about ziprasidone (Geodon), which is the antipsychotic most similar to lurasidone.

Half-life of lurasidone is 18 to 40 hours. It is dosed once daily with at least 350 calories, usually with the evening meal. Food is necessary for absorption. Compare this to ziprasidone, which must be given with food for the same reason, but ziprasidone has a shorter half-life, necessitating twice daily dosing. Another advantage of lurasidone (over ziprasidone) is lack of QT prolongation. Most other antipsychotics prolong QT interval to some extent.

Despite these advantages, patients with schizophrenia in clinical trials were likely to discontinue treatment with Latuda, due to either lack of benefit and/or side effects. In the real world, Latuda is even more likely to be stopped due to cost.



Antipsychotics are represented with spooky mascots.

It is noteworthy that the SGAs that do not cause weight gain (Latuda and Geodon) are the most likely to be stopped, while those causing the most weight gain (Zyprexa and Clozapine) are the most likely to be continued.

Lurasidone is relatively more likely than other SGAs to cause extrapyramidal symptoms (EPS).

Lurasidone is almost exclusively metabolized by CYP3A4, making it highly vulnerable to kinetic interactions. With most substrate medications, interactions can be handled by adjusting the dose. With lurasidone, 3A4 interactions are of such high consequence that it is contraindicated with strong 3A4 inducers or inhibitors.

Although the patent for lurasidone has expired, it still costs over $1,200 monthly in the US. In 2019 the FDA granted five drugmakers permission to sell generic versions. These companies struck a deal with Latuda's manufacturer to keep generic lurasidone off the market until 2023. In Canada, the price of brand-name Latuda is less than $180 monthly, and generic lurasidone is available for less than $70.

Dosing: For schizophrenia, start 40 mg QD with evening meal, max 160 mg/day; For bipolar depression, start 20 mg QD with evening meal, max 120 mg/day. Decrease dose for hepatic insufficiency.

Lurasidone

40-160mg/pv

2.Lurasidoni (Latuda)

Cafer, 2020

Eniten lopetetut lääkkeet:

Antipsychotics approved for bipolar depression (2020), listed in order of apparent effectiveness:

Second generation antipsychotic	NNT*
Olanzapine/fluoxetine combo (Symbyax)	4
Lurasidone (Latuda)	5
Quetiapine XR (Seroquel XR)	6
Cariprazine (Vraylar)	7

*NNT = Number Needed to Treat, i.e., number of patients you need to treat for one patient to respond. The lower the NNT, the more effective the medication.

All-cause discontinuation of SGAs in clinical trials for schizophrenia, approximate rank from most to least likely to be stopped by doctor or patient:

- **Lurasidone (Latuda)** - most likely to be stopped
- Ziprasidone (Geodon) - slightly fewer discontinuations than lurasidone
- Iloperidone (Fanapt)
- Asenapine (Saphris)
- Quetiapine (Seroquel)
- Aripiprazole (Abilify)
- Risperidone (Risperdal)
- Paliperidone (Invega)
- Clozapine (Clozaril) - despite side effects and inconveniences, patients continue it because it is effective
- Olanzapine (Zyprexa) - effective and usually no issues other than weight gain and diabetes

The fish (our symbol for 3A4 substrate) is big because with lurasidone 3A4 interactions are a very big deal.

Lurasidone is **contraindicated** with strong 3A4 inDucers, because lurasidone will be useless due to rapid clearance, reducing lurasidone levels by about **6-fold:**

- Carbamazepine (Tegretol)
- Phenytoin (Dilantin)
- Phenobarbital (Luminal)
- St. John's wort
- Rifampin

6X

Lurasidone is also **contraindicated** with strong 3A4 inHibitors due to radically increased lurasidone levels, up to **8-fold**:

- Fluconazole and other -azole antifungals
- Clarithromycin (antibacterial)
- Ritonavir (antiretroviral for HIV)

8x

The minimal effective daily dose for schizophrenia is 40 mg. If coadministered with a **moderate** 3A4 inDucer, lurasidone may need to be titrated to a higher dose. If used with a moderate 3A4 inHibitor, give half of the usual dose.

Dynamic interactions:

- Antidopaminergic
- Extrapyramidal effects
- Sedation (moderate)
- Hypotensive effects
- Prolactin elevation (mild)

Kinetic interactions:

- 3A4 substrate (major)

page 16

3A4 substrate (major)

50

2.Lurasidoni (Latuda)

- Urea, Krea, plv, maksakokeet, diffi
- aikataulutetut kokeet

Jacobson , 2023

Lurasidone

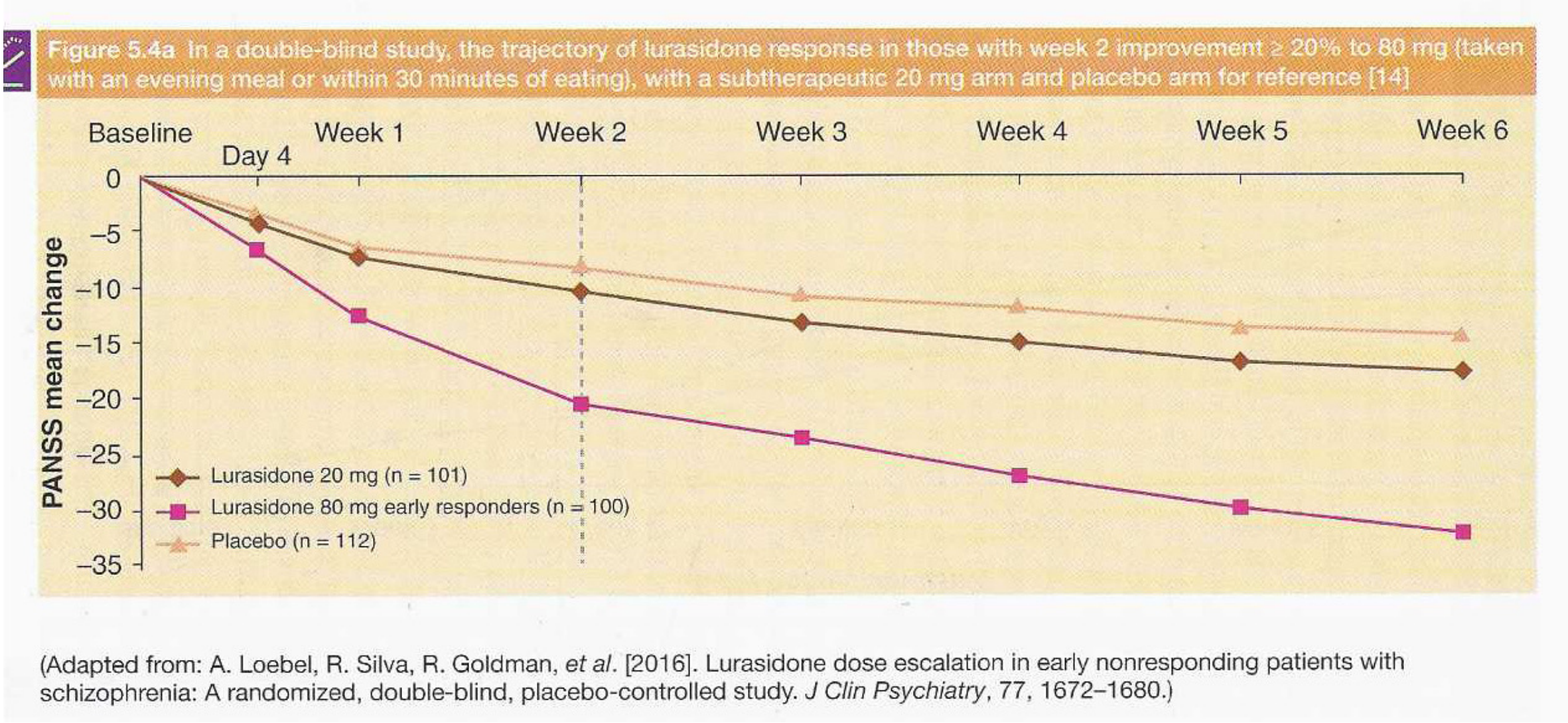
Screening laboratory tests	• BUN, creatinine, and urinalysis. Dosage adjustment is needed for moderate to severe renal impairment. • LFTs (AST, ALT, total bilirubin). Dosage adjustment is needed for patients with moderate to severe hepatic impairment. • CBC with differential. Low initial values for WBC count or ANC or any history of leukopenia or neutropenia increases the risk of a more severe reduction in blood counts. • Pregnancy testing for patients of childbearing potential Lurasidone has a relatively lower risk of causing the metabolic syndrome. Even so, metabolic screening and monitoring are recommended. Metabolic syndrome screening includes the following: • Fasting glucose • Fasting lipid profile (triglycerides and high-density lipoprotein) • Waist circumference • Blood pressure • Weight, height, and BMI calculation
Monitoring laboratory tests	• CBC with differential, BUN, creatinine, urinalysis, and LFTs at least annually. Metabolic syndrome monitoring: • Fasting glucose at 12 weeks, then yearly • Lipid profile at 12 weeks, then at least every 5 years • Waist circumference yearly • Blood pressure at 12 weeks, then every 6 months • Weight and BMI at 4 weeks, 8 weeks, and 12 weeks, then quarterly

American Society of Health-System Pharmacists: AHFS Drug Information. Bethesda, MD, American Society of Health-System Pharmacists, 2016

U.S. National Library of Medicine: Lurasidone hydrochloride tablet, film coated. DailyMed, May 17, 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1cc441b3-0a23-4c68-a90e-436030b7daf2. Accessed April 2022.

2.Lurasidoni (Latuda)

Meyer and Stahl , 2021

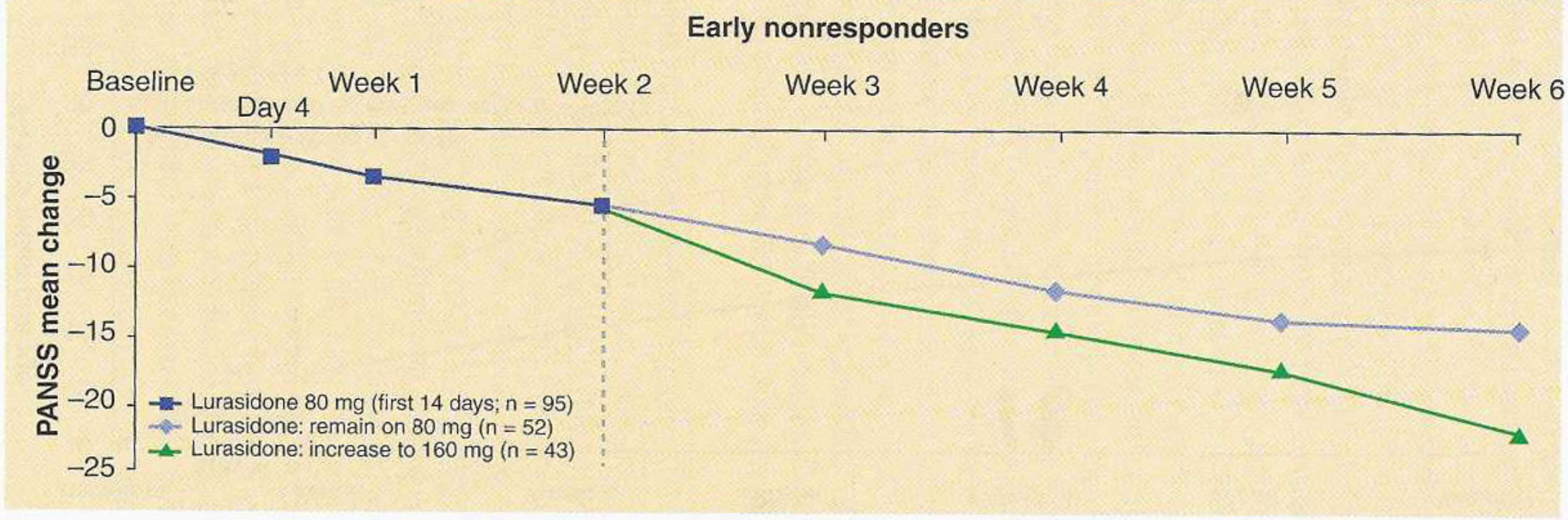


(Adapted from: A. Loebel, R. Silva, R. Goldman, *et al*. [2016]. Lurasidone dose escalation in early nonresponding patients with schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*, 77, 1672–1680.)

2.Lurasidoni (Latuda)

Meyer and Stahl , 2021

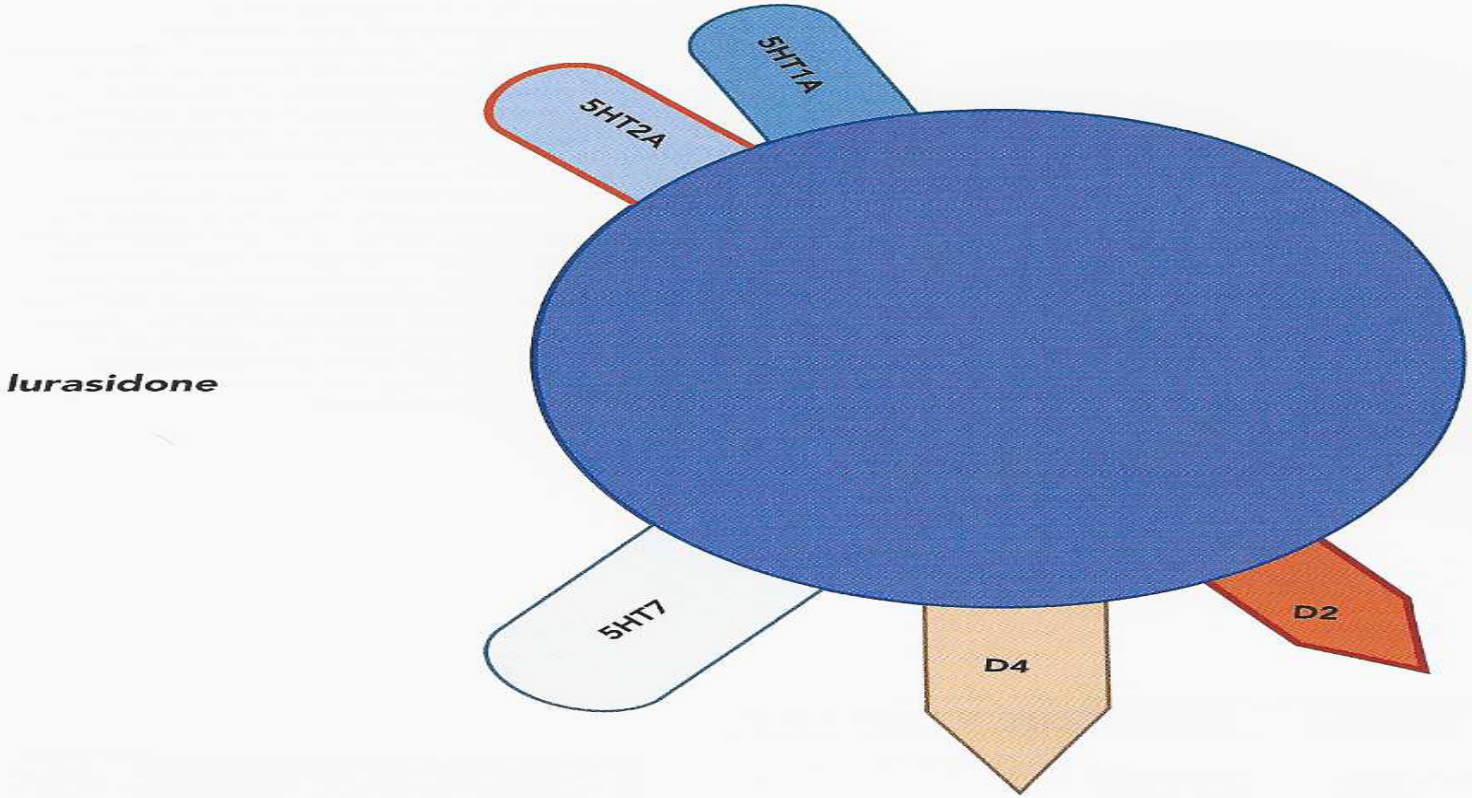
Figure 5.4b In a double-blind study, the trajectory of lurasidone response in those with week 2 improvement < 20% to 80 mg (taken with an evening meal or within 30 minutes of eating), all of whom were re-randomized 1:1 after the week 2 assessment to 80 mg or 160 mg (taken with an evening meal or within 30 minutes of eating) [14]



(Adapted from: A. Loebel, R. Silva, R. Goldman, *et al*. [2016]. Lurasidone dose escalation in early nonresponding patients with schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*, 77, 1672–1680.)

2.Lurasidoni (Latuda)

Stahl , 2021



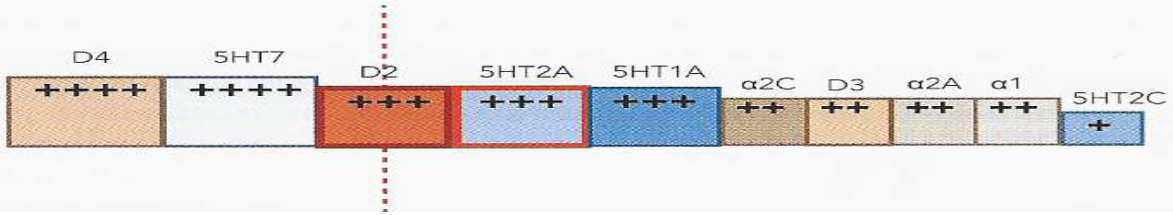


Figure 5-53 Lurasidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lurasidone. Lurasidone has a relatively simple pharmacological profile. It binds most potently to the D_4 receptor, the effects of which are not well understood, and to the $5HT_7$ receptor, which may contribute to efficacy for mood, cognitive, and sleep symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

3. Brekspipratsoli (Rxulti)

3. Brekspipratsoli (Rxulti)

- uusi Abilify?, titraus

BREXPIPRAZOLE (Rexulti) Fact Sheet

Bottom Line:
Rexulti may just be a newer spin on Abilify, which is now available as generic. More trial data, especially long-term and compared to other antipsychotic agents, will indicate whether this is a different chemical entity that warrants a much higher price tag. Until then, stick to the cheaper, generic aripiprazole.

FDA Indications:
Schizophrenia; depression adjunct.

Off-Label Uses:
Too new to tell.

Dosage Forms:
Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg.

Dosage Guidance:
- Schizophrenia: Start 1 mg/day on days 1–4; ↑ to 2 mg/day on days 5–7; then up to max 4 mg/day based on patient response. Usual dose 2 mg–4 mg/day.
- Depression adjunct: Start 0.5 mg–1 mg/day, ↑ at weekly intervals up to target 2 mg/day, max 3 mg/day.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Puzantian T and Carlat D, 2020

3. Brekspipratsoli (Rxulti)

Sivuvaikutus: painonnousu, akatitisia, uneliaisuus
T ½ = 91 tuntia (19 vuorokautta steady state)
Kerran päivässä , 2mg sama kuin placebo

Side Effects:

- Most common: Weight gain, akathisia, somnolence.
- Serious but rare: Rare reports of reversible pathologic gambling and other impulse control problems (eating, spending, sexual).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT1A receptor partial agonist and serotonin 5-HT2A receptor antagonist.
- Metabolized by CYP2D6 and 3A4; t ½: 91 hours.
- Use ½ usual dose in presence of 2D6 or 3A4 inhibitors or in known 2D6 poor metabolizers; ¼ dose if both 2D6 inhibitor/poor metabolizer and 3A4 inhibitors; double dose if also using 3A4 inducer.

Clinical Pearls:

- As the name suggests, brexpiprazole is chemically and structurally related to its manufacturer's previous blockbuster aripiprazole (Abilify).
- Although the FDA-approved target dose for schizophrenia is 2–4 mg/day, 2 mg/day was no better than placebo in one of two preclinical registration studies.
- Once-a-day dosing with no regard to meals makes this an easy-to-use option.

Fun Fact:

Plan on seeing more trial results with Rexulti in the future, including those in patients with ADHD, PTSD, and agitation associated with Alzheimer's dementia.

Puzantian T and Carlat D, 2020

3. Brekspipratsoli (Rxulti)

Vähemmän akatitisia kuin Abilify?

Cafer, 2020

2015
$1,154–$1,351

Brexpiprazole (REXULTI)

brex PIP ra zole / rex UL tee

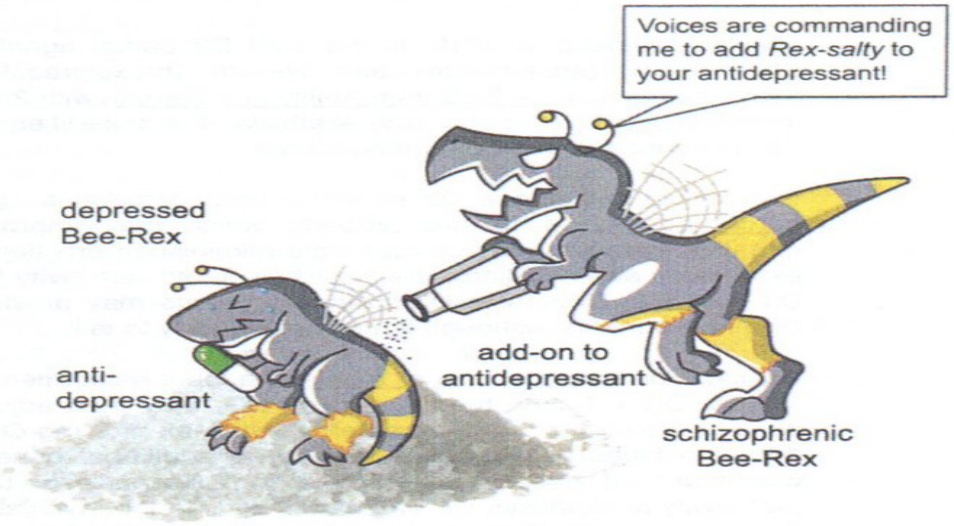
"Bee-Rex (Rex-salty)"

- Antipsychotic (SGA)
- D2 partial agonist - ⇔ DA
- 5-HT$_{1A}$ partial agonist - ⇔ DA
- 5-HT$_{2A}$ antagonist - ⇳ DA

0.25
0.5
1
2
3
4 mg

FDA-approved for:

- Schizophrenia
- Adjunct for major depression



Brexpiprazole (Rexulti) was released in 2015 by the makers of aripiprazole (Abilify) as Abilify's patent was expiring. Rexulti has the same mechanism of action—dopamine D2 partial agonist, serotonin 5-HT$_{1A}$ partial agonist and serotonin 5-HT$_{2A}$ antagonist. It has been described as a Serotonin-Dopamine Activity Modulator.

Compared to Abilify, Rexulti has lower affinity for D2 receptors, thereby causing significantly less akathisia than Abilify. Rexulti has much higher affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors, which may improve tolerability and contribute some anxiolytic effect.

Rexulti is FDA-approved for schizophrenia and as an adjunct to antidepressants for treatment of major depressive disorder (MDD).

Like Abilify, Rexulti is not expected to cause sedation.

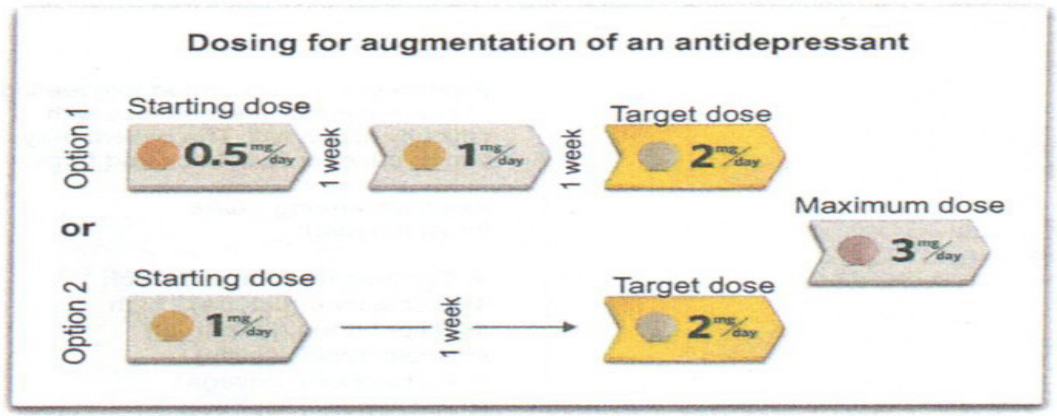
Rexulti may be associated with more weight gain than Abilify. It does not lower prolactin (as does aripiprazole) but does not elevate prolactin to a clinically significant extent. Other side effects may include nausea, headaches, and dizziness.

Dosing: The recommended dose of Rexulti depends on the indication. For schizophrenia, the dose is higher, and the titration is faster than if augmenting an antidepressant. See below for details. It can be taken at morning or night, with or without food. As with most antipsychotics, discontinue if absolute neutrophil count (ANC) drops below 1,000.

SGAs

3. Brekspipratsoli (Rxulti)

Cafer, 2020



13

5-HT_{1A} serotonin receptor agonists:

- Trazodone - antidepressant
- Nefazodone - antidepressant
- Flibanserin - libido enhancer

5-HT_{1A} serotonin receptor partial agonists:

- Buspirone - anxiolytic
- Aripiprazole - antipsychotic
- **Brexpiprazole** - antipsychotic
- Cariprazine - antipsychotic
- Vilazodone - antidepressant
- Vortioxetine - antidepressant

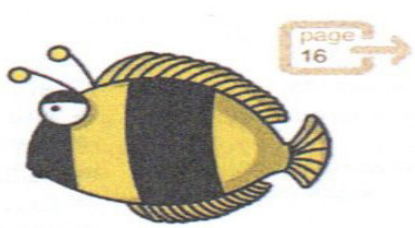
Dynamic interactions:

- Antidopaminergic (balanced)
- EPS (low)
- CNS depression (minimal)
- Hypotensive effects (mild)
- Hyperglycemia (possible)
- Weight gain (possible)

Kinetic interactions:

- 2D6 substrate (major)
- 3A4 substrate (major)

When used to augment the strong 2D6 inHibitors fluoxetine (Prozac) or paroxetine (Paxil), it is recommended brexpiprazole not exceed 2 mg.



3A4 substrate

2D6 substrate

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3. Brekspipratsoli (Rxulti)

Munuais- ja maksakokeet
Sokeri- ja rasvakokeet ja paino
Diffi (WBC = valkosolumäärä ja ANC =absol neutr määrä)

Jacobson , 2023

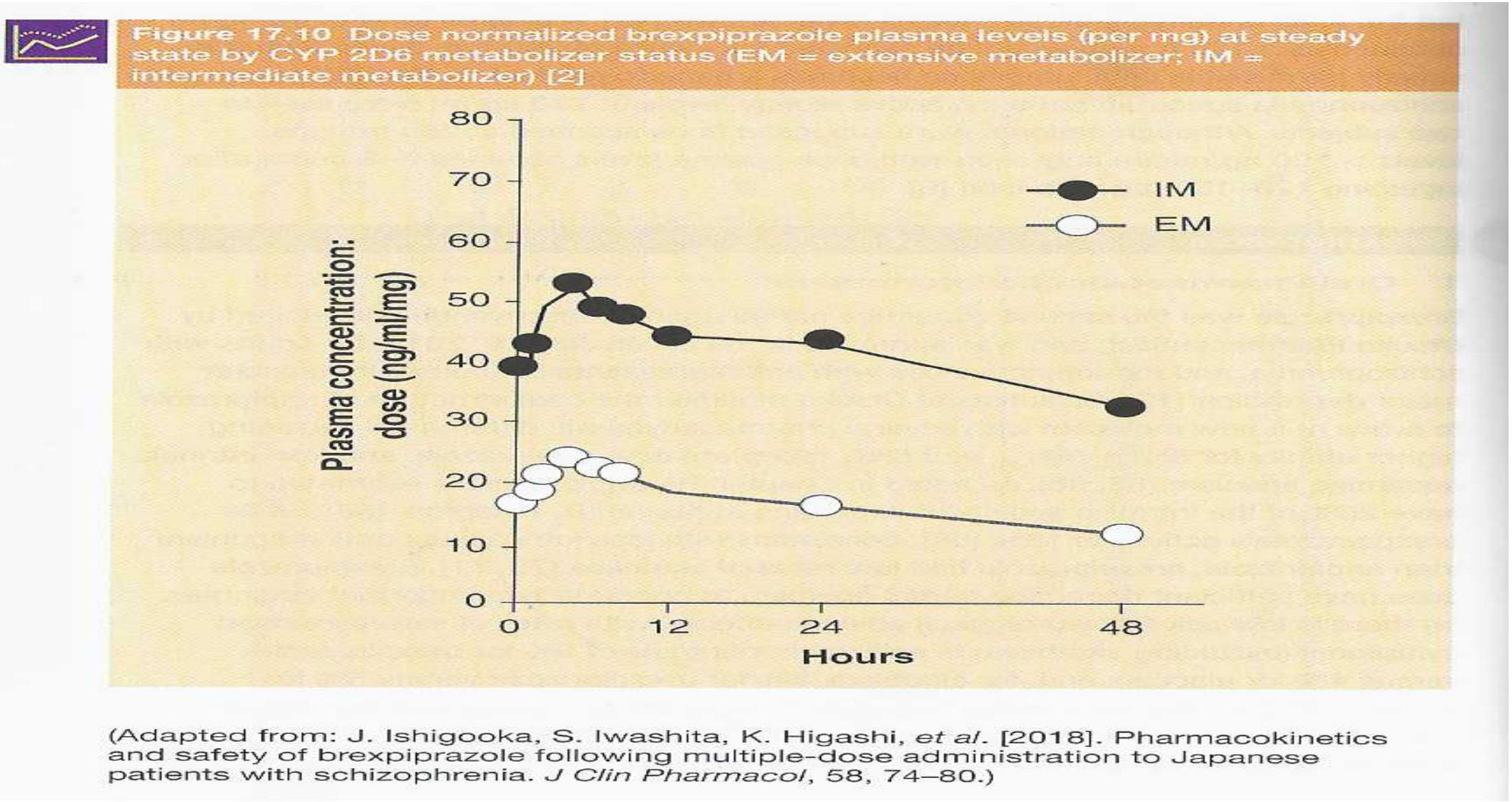
Brexpiprazole

Screening laboratory tests	• Evaluate baseline renal and hepatic function. Dosage adjustment is required for moderate to severe impairment. • Obtain baseline fasting glucose, lipid profile, and weight. Metabolic parameters may be affected by brexpiprazole. • Obtain baseline WBC count and differential. Preexisting leukopenia or neutropenia is a risk factor for significant decline in these values. If baseline values are low or the patient has a history of drug-induced leukopenia/neutropenia, obtain CBC with differential.
Monitoring laboratory tests	• Periodic monitoring of metabolic parameters: fasting glucose, lipid profile, and weight. • Obtain CBC with differential frequently during the first few months of therapy for patients with a low baseline WBC count or ANC or a history of drug-induced leukopenia/neutropenia. • If ANC is $<1{,}000/mm^3$, discontinue drug and follow WBC count until recovery.

U.S. Food and Drug Administration: Rexulti (brexpiprazole) package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205422s003lbl.pdf. Accessed April 2022.

3. Brekspipratsoli (Rxulti)

Meyer and Stahl , 2021



3. Brekspipratsoli (Rxulti)

Stahl , 2021

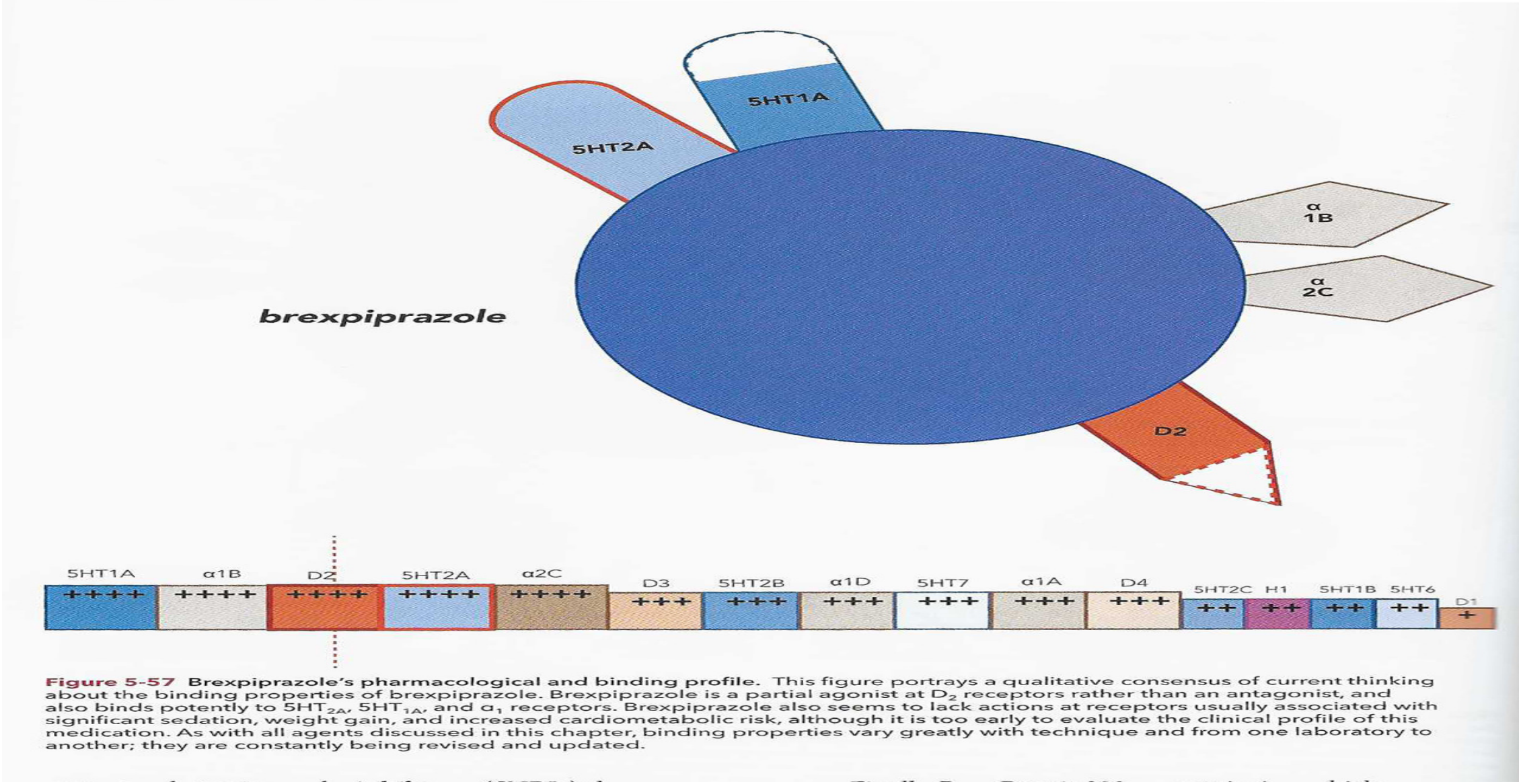


Figure 5-57 **Brexpiprazole's pharmacological and binding profile.** This figure portrays a qualitative consensus of current thinking about the binding properties of brexpiprazole. Brexpiprazole is a partial agonist at D_2 receptors rather than an antagonist, and also binds potently to $5HT_{2A}$, $5HT_{1A}$, and α_1 receptors. Brexpiprazole also seems to lack actions at receptors usually associated with significant sedation, weight gain, and increased cardiometabolic risk, although it is too early to evaluate the clinical profile of this medication. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

4. Karipratsiini (Reagila)

4. Karipratsiini (Reagila)

CARIPRAZINE (Vraylar) Fact Sheet

Bottom Line:
Cariprazine's potential claim to fame will be efficacy for negative symptoms, but the data are too preliminary to make a definitive conclusion. Beyond that, it appears to be another in a series of me-too antipsychotics, with a side effect profile heavy on EPS and akathisia as well as significant potential for weight gain.

FDA Indications:
Schizophrenia; acute treatment of **bipolar disorder (manic or mixed episodes); bipolar depression.**

Off-Label Uses:
Negative symptoms of schizophrenia; major depression.

Dosage Forms:
Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg.

Dosage Guidance:
- Schizophrenia and bipolar disorder: Start 1.5 mg/day, increase to 3 mg/day as early as 2nd day. Adjust by 1.5 mg–3 mg/day increments to usual dose 1.5 mg–6 mg/day in schizophrenia and 3 mg–6 mg/day in bipolar disorder.
- Bipolar depression: Start 1.5 mg QD. May increase to 3 mg QD after 2 weeks or longer; max dose 3 mg/day.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Puzantian T and Carlat D, 2020

4. Karipratsiini (Reagila)

T ½ aktiivinen metaboliitti: 1-3 viikkoa; steady state 5-15 viikoa

Antipsychotics

Side Effects:

- Most common: EPS, akathisia, weight gain, sedation.
- Serious but rare: See class warnings in chapter introduction.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and D3 and serotonin 5-HT1A receptor partial agonist; serotonin 5-HT2A receptor antagonist.
- Metabolized primarily by CYP3A4; t ½: 2–4 days for cariprazine (1–3 weeks for active metabolites).
- Caution with CYP3A4 inhibitors; 50% dose reduction may be necessary. Avoid use with 3A4 inducers.

Clinical Pearls:

- Most recently approved atypical antipsychotic. Most closely similar to aripiprazole with partial D2 agonism.
- Manufacturer and very early data suggest D3 activity may result in negative symptom improvement.

Fun Fact:

Cariprazine was developed by a Hungarian pharmaceutical company, Gedeon Richter, which was founded in 1901 by a pharmacist. It initially processed extracts from plants to produce herbal drugs.

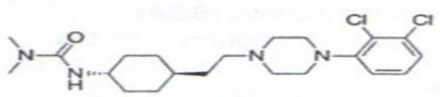
Puzantian T and Carlat D, 2020

4. Karipratsiini (Reagila)

1.5 mg päivä, sitten 3mg pv ad 6mg

Cafer, 2020

2016
$1,189–$1,452

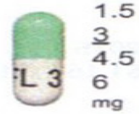


Cariprazine (VRAYLAR)

kar IP ra zeen / va RAY lar

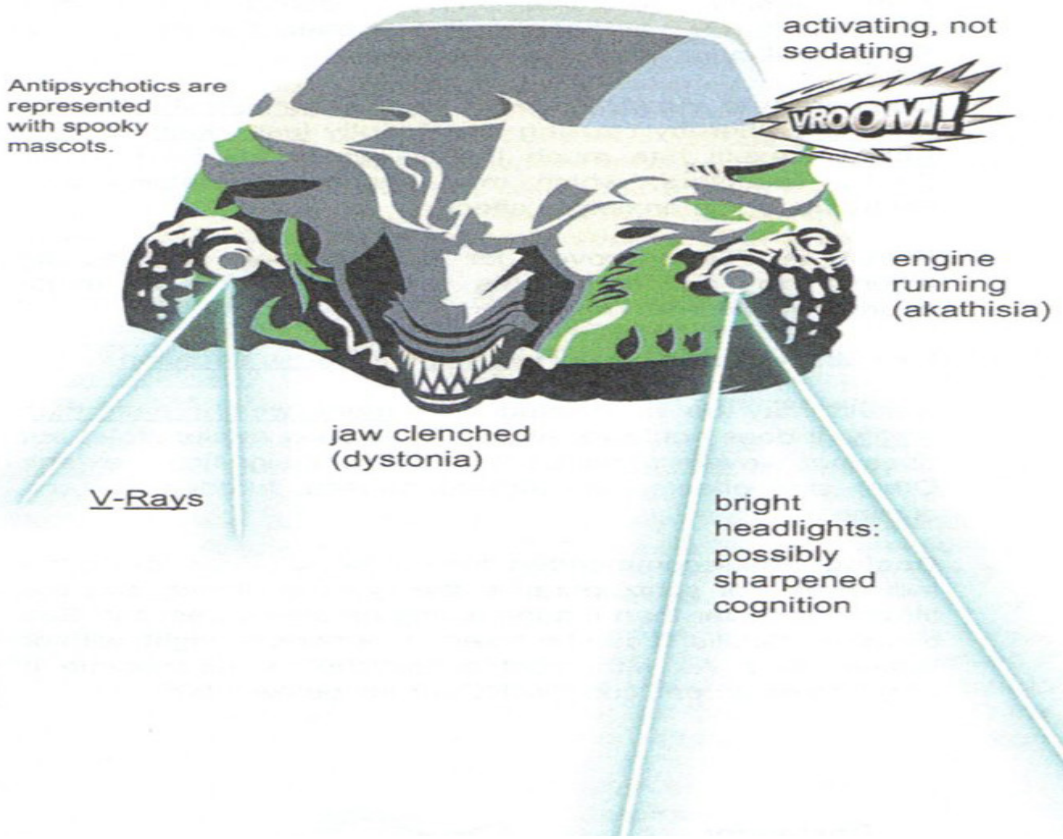
"Car ripper seen (going) Vroom!"

- Antipsychotic (SGA)
- D2 partial agonist - ⇔ DA
- D3 partial agonist - ⇔ DA
- 5-HT$_{1A}$ partial agonist - ⇔ DA
- 5-HT$_{2A}$ antagonist - ⇧ DA



1.5
3
4.5
6
mg

Take your pick of mnemonics: *"Car ripper seen (going) Vroom!", "Car's V-rays", "Car ripper praising V-rays".*



FDA-approved for
- Schizophrenia
- Bipolar I Disorder, manic/mixed episode
- Bipolar I Disorder, depressive episode

Used off-label for:
- Bipolar maintenance

Vraylar, released in 2016, is the third D2 partial agonist, after Abilify (aripiprazole) and Rexulti (brexpiprazole). Vraylar causes more EPS than Abilify and Rexulti, with 25% incidence of dystonia and 15% akathisia. It is more likely to cause nausea than other antipsychotics.

In addition to being a D2 partial agonist, Vraylar is D3 partial agonist, a unique property which may improve negative symptoms of schizophrenia (diminished emotional expression and avolition). Vraylar has a 5-fold selectivity for D3 over D2. Dopamine D3-preferring agents may provide cognitive benefits, although it may be too early to tell.

Dosing: For schizophrenia or mania, the label recommends 1.5 mg QD x 1 day, then 3 mg PO QD; May then adjust dose in 1.5 mg or 3 mg increments with max of 6 mg QD. Although higher doses were tested, no additional benefit was found at doses exceeding 6 mg; Because of the probability of akathisia, Dr. Tammas Kelly (Carlat Psychiatry Report, Aug 2019) recommends titrating more slowly, starting 1.5 mg QOD, increasing to 1.5 mg QD after a week. For bipolar depression the dose is 1.5 mg QD; At 14 days increase to the maximum dose for depression of 3 mg QD. However, the sweet spot for depression seems to be 1.5 mg, 3 mg causes more side effects without much additional benefit. As with most antipsychotics, discontinue if absolute neutrophil count (ANC) drops below 1,000.

Cariprazine Paliperi

4. Karipratsiini (Reagila)

Cafer, 2020

peridone

Long headlights: Vraylar has the longest half-life of all antipsychotics, about 14 days for the main active metabolite.

The Vraylar television ad showed a house of cards as a metaphor for mania, which may feel great to an individual with bipolar disorder until the inevitable crash to depression.

Side effect profile for D2 partial agonists:

Akathisia (common)	Vraylar > Abilify > Rexulti
Weight gain (minimal/ modest)	Rexulti > Abilify > **Vraylar**
Somnolence (minimal)	Abilify > Rexulti > Vraylar

Dynamic interactions:
- Antidopaminergic (balanced)
- EPS
- CNS depression (minimal)
- Hypotensive effects (mild)

Kinetic interactions:
- 3A4 substrate (major)
- The concentration of Vraylar is doubled by 3A4 inHibitors
- Avoid prescribing with 3A4 inDucers because Vraylar will be cleared too quickly

page 16

3A4 substrate (major)

54

Akatitisiaa eniten:

Akathisia is an uncomfortable feeling of internal motor restlessness with difficulty sitting still. The patient may fidget, pace, or rock back and forth.

Akathisia among SGAs (most to least):

- Cariprazine (Vraylar) - high
- Lurasidone (Latuda) - high
- Risperidone (Risperdal)
- Aripiprazole (Abilify)
- Paliperidone (Invega)
- Asenapine (Saphris)
- Ziprasidone (Geodon)
- Olanzapine (Zyprexa)
- Brexpiprazole (Rexulti) - low
- Pimavanserin (Nuplazid) - low
- Iloperidone (Fanapt)
  - marketed for those with akathisia
- Clozapine (Clozaril) - very low
- Quetiapine (Seroquel) - least

4. Karipratsiini (Reagila)

Jacobson, 2023

Diffi, maksakokeet, urea, Krea
- ei maksa- eikä munuaissairaille
-sokeri- ja rasvakokeet ja paino

Cariprazine

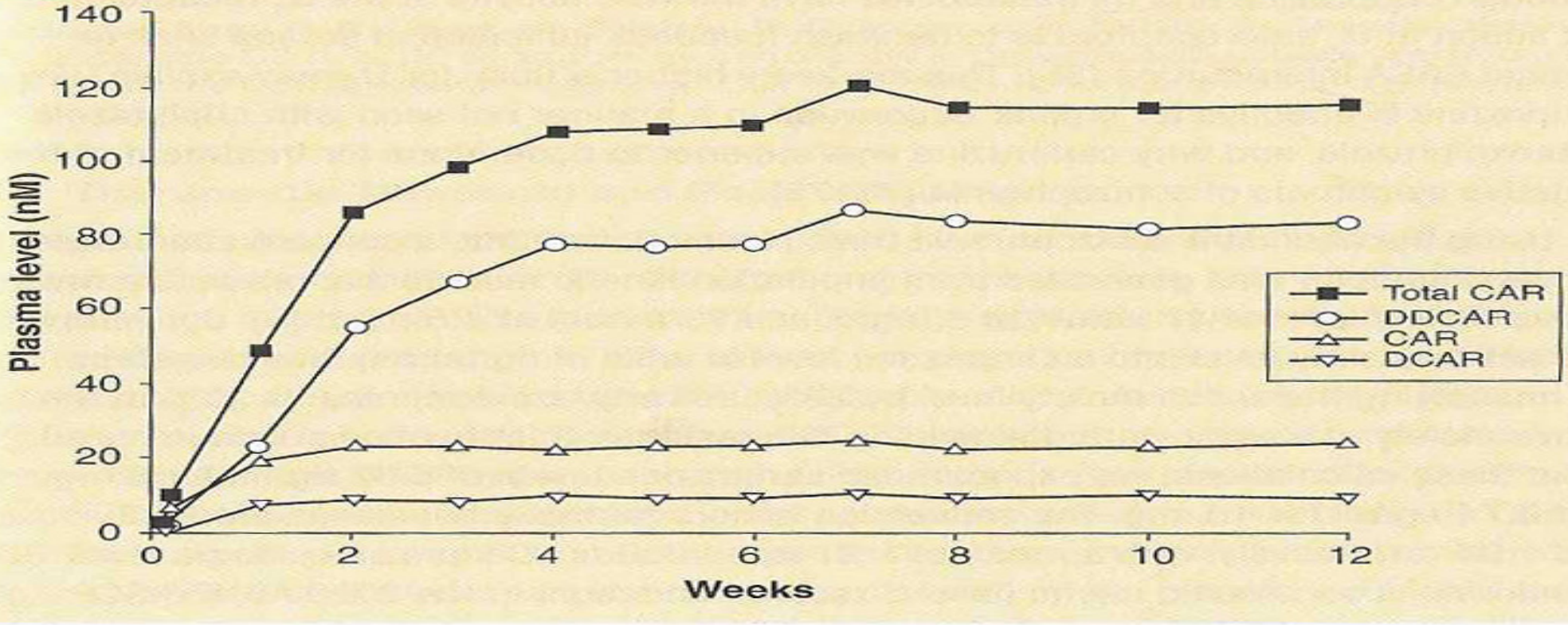
Screening laboratory tests	• CBC with differential. Leukopenia and neutropenia have been reported with this drug, and low baseline values increase this risk. • Consider LFTs, BUN, and creatinine. Drug is not recommended in patients with severe hepatic or renal impairment. • Fasting glucose, lipid profile, and weight to establish baseline values.
Monitoring laboratory tests	• Periodic check of CBC with differential. In patients with low baseline WBC count or ANC, check CBC with differential frequently during the first few months of treatment. Discontinue the drug in patients with an ANC $<1{,}000/mm^3$ and follow the WBC count until recovery. • Soon after initiation of the drug and periodically during treatment, check patient's fasting glucose and lipid profile and obtain weight.

U.S. National Library of Medicine: DailyMed: Vraylar: cariprazine capsule, gelatin coated. DailyMed, July 15, 2021 Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3435ec73-86ed-46d1-bd1f-ee6c30209123. Accessed April 2022.

4. Karipratsiini (Reagila)

Meyer and Stahl, 2021

Figure 17.12 Kinetic profile of oral cariprazine (CAR) 6 mg/d showing the contributions of the two metabolites desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) [13]



(Adapted from: Allergan USA Inc. [2019]. Vraylar package insert. Madison, NJ.)

4. Karipratsiini (Reagila)

Stahl, 2021

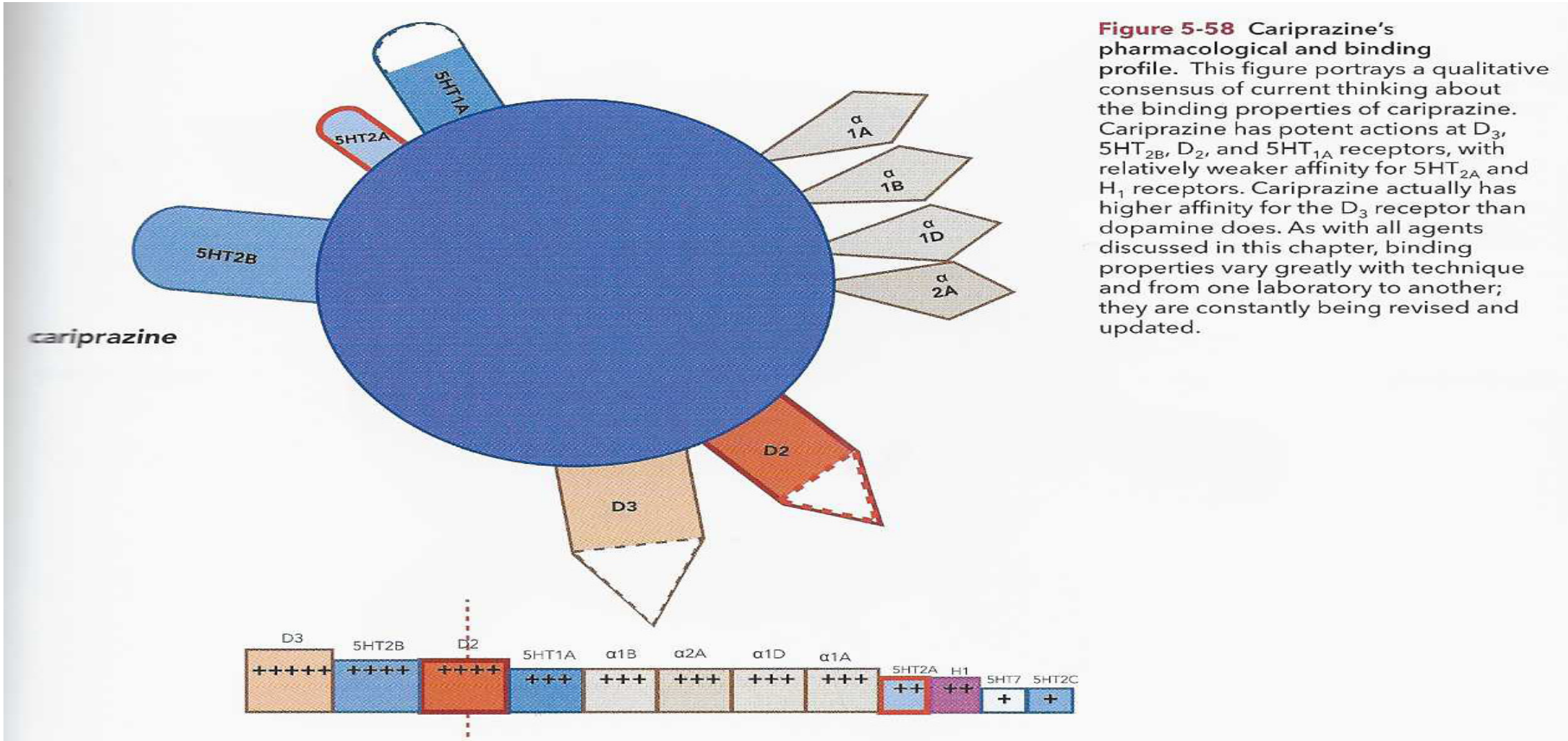


Figure 5-58 Cariprazine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of cariprazine. Cariprazine has potent actions at D_3, $5HT_{2B}$, D_2, and $5HT_{1A}$ receptors, with relatively weaker affinity for $5HT_{2A}$ and H_1 receptors. Cariprazine actually has higher affinity for the D_3 receptor than dopamine does. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

5. Pimavanseriini (Nuplazid)

5. Pimavanseriini (Nuplazid)

Parkinson ja dementia psykoosit
- ketiapiini ja klotsapiini

PIMAVANSERIN (Nuplazid) Fact Sheet

Bottom Line:
Pimavanserin is the only approved medication for psychosis in Parkinson's disease, but we do not yet know if it has any efficacy advantages over quetiapine, which has generally been the go-to antipsychotic for this syndrome. The fact that it does not cause weight gain is a side effect advantage, but the controversy around safety is somewhat concerning.

FDA Indications:
Hallucinations and delusions associated with Parkinson's disease psychosis.

Off-Label Uses:
Too new to tell.

Dosage Forms:
Tablets: 10 mg.
Capsules: 34 mg.

Dosage Guidance:
Start and continue with 34 mg once daily (no titration). Use 10 mg tablet in patients taking concurrent CYP3A4 inhibitors.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Puzantian T and Carlat D, 2020

5. Pimavanseriini (Nuplazid)

T1/2 on 57 (200)h eli lähes 12 pv steady state
QTC pidentyminen!
- ei vaikuta dopamiinireseptoreihin

Side Effects:

- Most common: Nausea, peripheral edema, confusion.
- Serious but rare: QT prolongation (dose related; mean prolongation of 5–8 msec at usual dose); class warning regarding increased mortality in elderly.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Atypical antipsychotic with combination of inverse agonist and antagonist activity at 5-HT2A and, less so, at 5-HT2C receptors.
- Metabolized by CYP3A4 and 3A5; t ½: 57 hours (200 hours for active metabolite).
- Caution with potent inhibitors or inducers of 3A4 (adjust dose per above). Avoid use with other medications that may increase QT interval.

Clinical Pearls:

- FDA approval based on one 6-week placebo-controlled outpatient study of 185 patients that showed only modest (but statistically significant) improvement in hallucinations and delusions compared to placebo.
- The study didn't find any difference (improvement or worsening) in motor function between those who received Nuplazid or placebo.
- All in all though, Nuplazid did not show statistically significant benefit in three out of four pre-approval clinical studies.
- Reports of post-marketing deaths in patients who had taken Nuplazid have sparked investigation and controversy, though we still don't know if it's any more dangerous than clozapine or quetiapine use in Parkinson's.

Fun Fact:

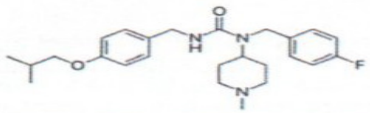
Unlike other atypical antipsychotics, Nuplazid does not have effects on dopamine receptors, and this may contribute to the finding that it doesn't worsen motor symptoms in Parkinson's.

Puzantian T and Carlat D, 2020

5. Pimavanseriini (Nuplazid)

Cafer, 2020

2017
$2,741–$3,097



Pimavanserin (NUPLAZID)

PIM a VAN ser in / Nu PLAHZ id

"Pima van (New plaster)"

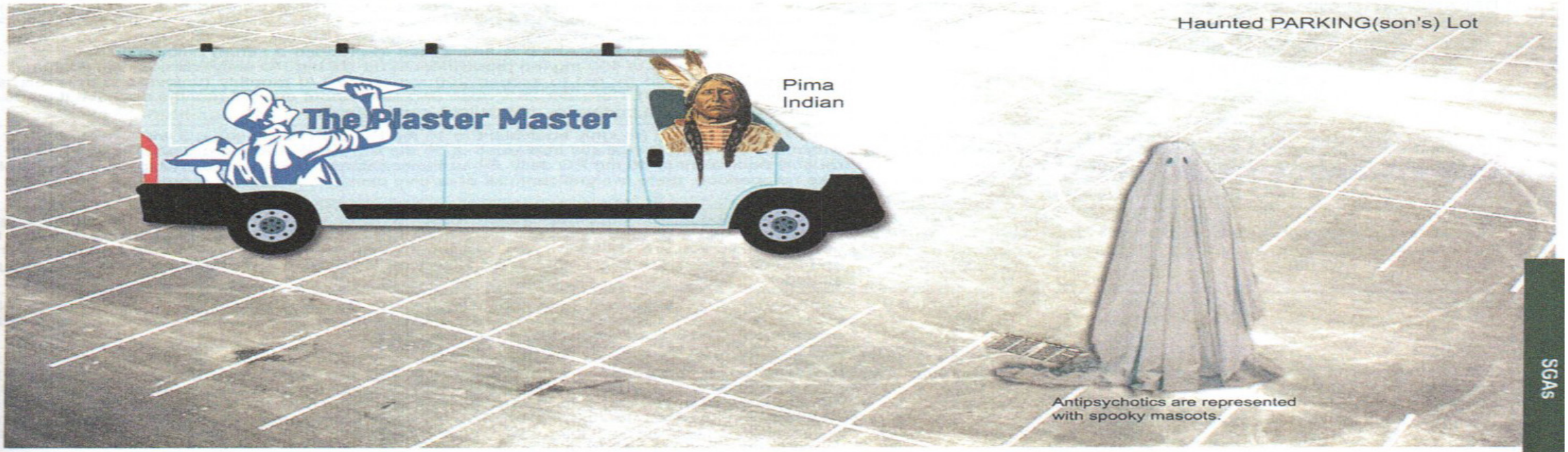
- Novel antipsychotic
- Nondopaminergic
- 5-HT_{2A} inverse agonist

10 tab
17 tab
34 mg cap

FDA-approved for:

- Psychosis associated with Parkinson's disease

Pimavanserin (Nuplazid), released in 2017, is FDA-approved for hallucinations and delusions associated with Parkinson's disease. Up to 50% of patients with Parkinson's disease develop these problems. Some sources refer to pimavanserin as a second generation antipsychotic (SGA), but its antipsychotic mechanism is entirely different from other medications in this class.



5. Pimavanseriini (Nuplazid) Kuolemariski ! Cafer, 2020

Pimavanserin is the only available antipsychotic that does not act on dopamine receptors (unless you count cannabidiol). This makes pimavanserin ideal for Parkinson's disease, which is aggravated by dopamine blockade. Pimavanserin has a relatively unique mechanism as a selective serotonin inverse agonist that preferentially targets 5-HT_{2A} receptors. By definition, an inverse agonist binds to a receptor and produces effects opposite to those of an agonist. The effect of the inverse agonist can be blocked by an antagonist. A few other medications in this book are inverse agonists (among other mechanisms) but we refer to them as antagonists for simplicity.

Prior to pimavanserin the antipsychotic of choice for individuals with Parkinson's disease was quetiapine (Seroquel), which causes little to no extrapyramidal symptoms (EPS). Clozapine (Clozaril), which does not cause EPS, would be a good choice for this population if not for its numerous health risks and lab monitoring requirements.

Side effects of pimavanserin include peripheral edema (7%) and nausea (7%). It can cause angioedema, i.e., localized non-pitting edema of deep dermis and subcutaneous tissue. Pimavanserin may modestly prolong QT interval, but otherwise does not have side effects associated with other antipsychotics such as sedation, weight gain, constipation, gynecomastia or neutropenia.

All antipsychotics, pimavanserin included, carry a black box warning of increased mortality in elderly patients with dementia-related psychosis. For pimavanserin, the warning reads "not approved for dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis". Over the course of a 10-week controlled trial for the intended population, the rate of death was 4.5%, compared to a 2.6% in placebo-treated patients. Most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia). Exercise caution

in patients with uncorrected electrolyte abnormalities or any type of heart condition (recent heart attack, congestive heart failure, arrhythmia, bradycardia, etc.)

13

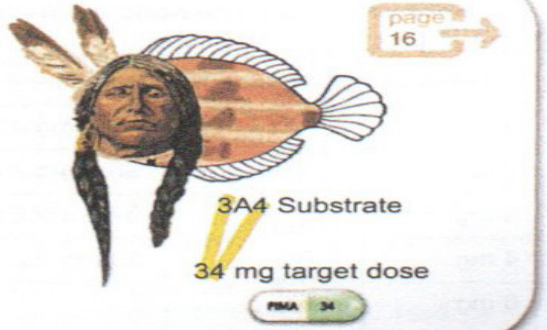
Nasrallah et al (2019) demonstrated successful treatment of clozapine-resistant psychosis with pimavanserin in individuals without Parkinson's disease. It appears to improve negative symptoms of schizophrenia (diminished emotional expression and avolition). Pimavanserin has potential for treatment-resistant depression as an adjunct to an SSRI or SNRI (Fava et al, 2019).

Oddly, the 10 mg and 17 mg pills are tablets while the 34 mg pill is a capsule.

Dosing: Start at 34 mg once daily, which is the target dose. Titration is unnecessary. In the presence of a strong 3A4 inhibitor, use a half strength dose of pimavanserin. With a strong 3A4 inducer, monitor for efficacy and exceed 34 mg if necessary.

Dynamic interactions:
- QT prolongation (low risk)

Kinetic interactions:
- 3A4 substrate (major)
  - dose adjustments apply (see above)



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5. Pimavanseriini (Nuplazid)

EKG!, Na, Mg

Jacobson, 2023

Pimavanserin

Screening laboratory tests	• ECG to establish baseline QTc and exclude bradycardia and any cardiac arrhythmias. • Consider electrolytes (potassium and magnesium). Low levels increase the risk of *torsades de pointes* and/or sudden death in the presence of QTc prolongation.
Monitoring laboratory tests	ECG annually or more often in presence of QTc prolongation or cardiac symptoms

U.S. National Library of Medicine: Nuplazid: pimavanserin tartrate capsule. DailyMed, February 8, 2022. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e6bea44-57d6-4bac-9328-46e1ee59f83b. Accessed April 2022.

5. Pimavanseriini (Nuplazid)

Stahl, 2021

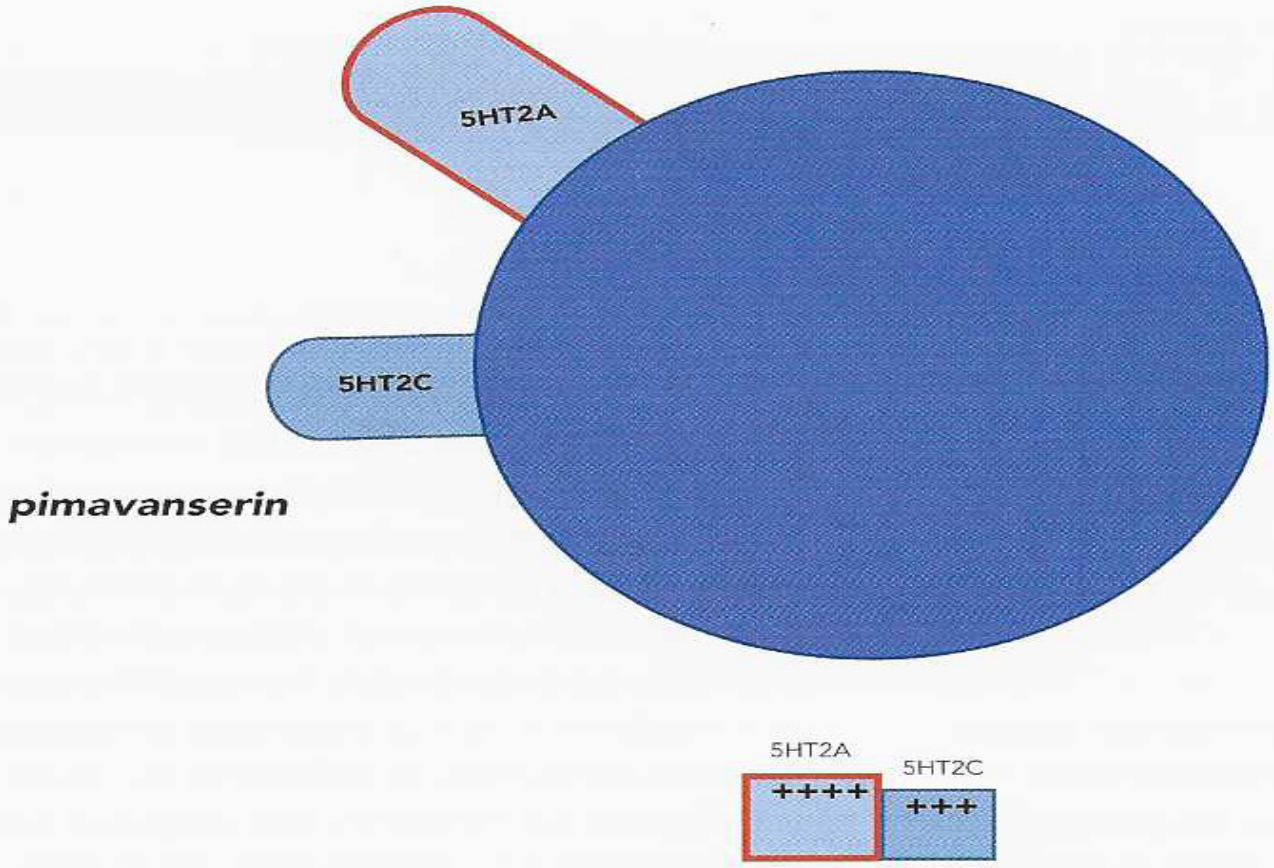


Figure 5-59 Pimavanserin's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of pimavanserin. Pimavanserin is the only known drug with proven antipsychotic efficacy that does not bind to D_2 receptors. Instead, it has potent $5HT_{2A}$ antagonism (sometimes called inverse agonism) with lesser $5HT_{2C}$ antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

6. Iloperidoni (Fanaptum)

6. Iloperidoni (Fanaptum)

2x pvssä, QTC ongelmat,
painonnousu, verensokeriongelmat
uneliaisuus

ILOPERIDONE (Fanapt) Fact Sheet

Bottom Line:
Not recommended as first-choice agent due to twice-daily dosing, need for titration, QT prolongation (comparable to ziprasidone), dizziness, moderate weight gain, and increases in blood sugar; and because it appears less efficacious than other antipsychotics.

FDA Indications:
Schizophrenia.

Off-Label Uses:
Bipolar disorder; major depression; behavioral disturbances; impulse control disorders.

Dosage Forms:
Tablets: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg.

Dosage Guidance:
Start 1 mg BID; ↑ to 2 mg BID on day 2 and then daily by 4 mg/day to a target dose of 6 mg–12 mg BID daily; max 12 mg BID.

Monitoring: Fasting glucose, lipids.

Cost: $$$$$

Puzantian T and Carlat D, 2020

6. Iloperidoni (Fanaptum)

T1/2 91 tuntia eli 19 pv steady state
2 mg sama kuin placebo

Side Effects:

- Most common: Weight gain, akathisia, somnolence.
- Serious but rare: Rare reports of reversible pathologic gambling and other impulse control problems (eating, spending, sexual).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT1A receptor partial agonist and serotonin 5-HT2A receptor antagonist.
- Metabolized by CYP2D6 and 3A4; t ½: 91 hours.
- Use ½ usual dose in presence of 2D6 or 3A4 inhibitors or in known 2D6 poor metabolizers; ¼ dose if both 2D6 inhibitor/poor metabolizer and 3A4 inhibitors; double dose if also using 3A4 inducer.

Clinical Pearls:

- As the name suggests, brexpiprazole is chemically and structurally related to its manufacturer's previous blockbuster aripiprazole (Abilify).
- Although the FDA-approved target dose for schizophrenia is 2–4 mg/day, 2 mg/day was no better than placebo in one of two preclinical registration studies.
- Once-a-day dosing with no regard to meals makes this an easy-to-use option.

Fun Fact:

Plan on seeing more trial results with Rexulti in the future, including those in patients with ADHD, PTSD, and agitation associated with Alzheimer's dementia.

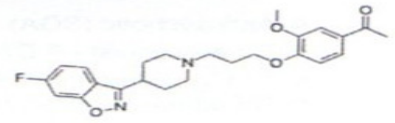
Puzantian T and Carlat D, 2020

6. Iloperidoni (Fanaptum)

- ortostaattinen hypotensio

Cafer, 2020

2009
$1,027–$1,116



Iloperidone (FANAPT)

eye loe PER i dohn / fan APT

"Fan Napped (with) Eye Opener"

- Antipsychotic (SGA)
- D2 antagonist - ⇩ DA
- 5-HT_{2A} antagonist - ⇩ DA

1
2
4
6
8
10
12 mg

FDA-approved for:
- Schizophrenia

Used off-label for:
- Bipolar disorder

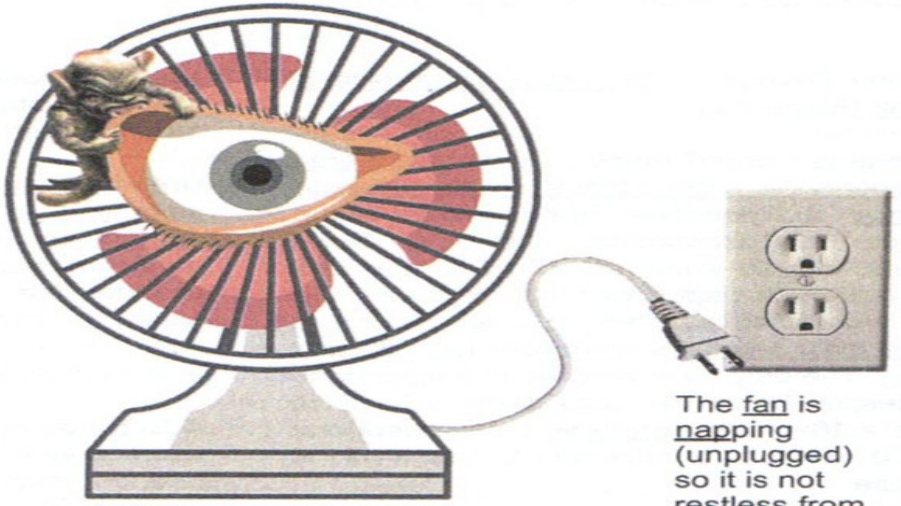
"(Look what that) Eye Opener done (while that) Fan Napped."

Iloperidone (Fanapt), released in 2009, is marketed for patients taking antipsychotic medication who can't sit still, because it has low incidence of akathisia. Fanapt's only FDA-approved indication is schizophrenia.

The starting dose must be titrated to avoid orthostatic hypotension. Among antipsychotics, Fanapt has relatively high potential for weight gain, a distant #3 behind olanzapine and clozapine—*Fanapt gives you a fat fanny.*

Among available SGAs, Fanapt has a relatively high tendency to prolong QT interval, #2 behind ziprasidone (Geodon) among SGAs. Although the risk of clinically significant QT prolongation is minimal, advertisements for Fanapt caution "in choosing among treatments, prescribers should consider the ability of Fanapt to prolong the QT interval and the use of other drugs first".

Half-life is about 18 hours. It should be discontinued if absolute neutrophil count (ANC) drops below 1000 or if there is an unexplained drop in WBC.



Antipsychotics are represented with spooky mascots.

The fan is napping (unplugged) so it is not restless from akathisia.

Dosing: See below for titration schedule. The titration pack contains #2 of 1 mg, #2 of 2 mg, #2 of 4 mg, and #2 of 6 mg tabs. The target dose for schizophrenia is 6–12 mg BID. Maximum 24 mg total daily dose. Adjust dose for kinetic interactions described below.

Iloperidone

6. Iloperidoni (Fanaptum)

Cafer, 2020

Asenapine

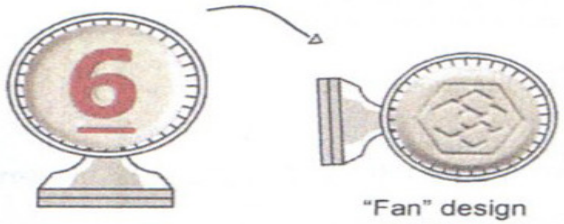
As a point of trivia, iloperidone shares a mechanism of action with the rarely prescribed tricyclic antidepressant (TCA) trimipramine (Surmontil).

Iloperidone failed the approval process in Europe for treatment of schizophrenia, because risks of the drugs were deemed to outweigh potential benefits.

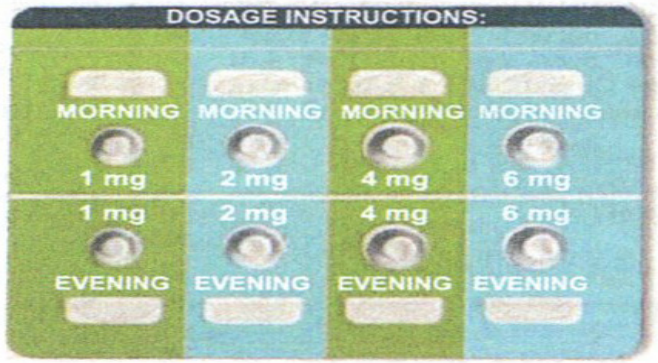
If started at 6 mg without titrating, the patient may pass out from hypotension.

Recommended titration:

Day one: 1 mg BID
Day two: 2 mg BID
Day three: 4 mg BID
Day four: 6 mg BID



Fanapt titration pack:



Dynamic interactions:

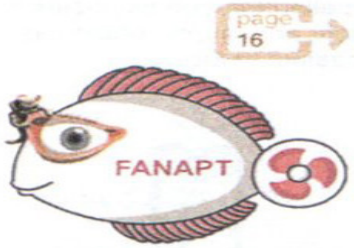
- Sedation
- Weight gain
- QT prolongation
- Dopamine antagonist
- Extrapyramidal effects
- Hypotensive effects
- Lowers seizure threshold

Kinetic interactions:

- 2D6 substrate
- 3A4 substrate

Levels of iloperidone are increased by 2D6 or 3A4 inHibitors, increasing the risk of QT prolongation. If a strong 2D6 or 3A4 inHibitor is in the pill box, use a ½ strength dose of iloperidone.

3A4 substrate



3A4 substrate

6. Iloperidoni (Fanaptum)

EKG, K, Na, metaboliakokeet
Diffi

Jacobson, 2023

Iloperidone

Screening laboratory tests	• ECG to determine baseline QTc. Drug prolongs the QT interval and may be associated with arrhythmia and sudden death. If baseline QTc is >500 msec, consider risks/benefits. • Serum potassium and magnesium levels to determine baseline. Hypokalemia and/or hypomagnesemia increase the risk of QT prolongation and arrhythmia. • Fasting glucose, lipid profile, and weight to determine baseline values. • CBC with differential. Low initial values for WBC count or ANC or any history of drug-induced neutropenia increases the risk of more severe neutropenia.
Monitoring laboratory tests	• Periodic ECG to determine QTc. If QTc is persistently >500 msec or increases >20 msec, consult cardiology and consider discontinuing drug. • Periodic serum potassium and magnesium levels • Periodic fasting glucose, lipid profile, and weight checks • Periodic check of CBC with differential. In patients with low baseline WBC count or ANC or a history of drug-induced neutropenia, check CBC with differential frequently during the first few months of treatment. Discontinue drug in patients with an ANC <1,000/mm^3 and follow WBC count until recovery.

American Society of Health-System Pharmacists: AHFS Drug Information. Bethesda, MD, American Society of Health-System Pharmacists, 2016

U.S. National Library of Medicine: Iloperidone tablet. DailyMed, August 2, 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6f17cc91-86b3-42e3-9bf2-935dd360c3eb. Accessed April 2022.

6. Iloperidoni (Fanaptum)

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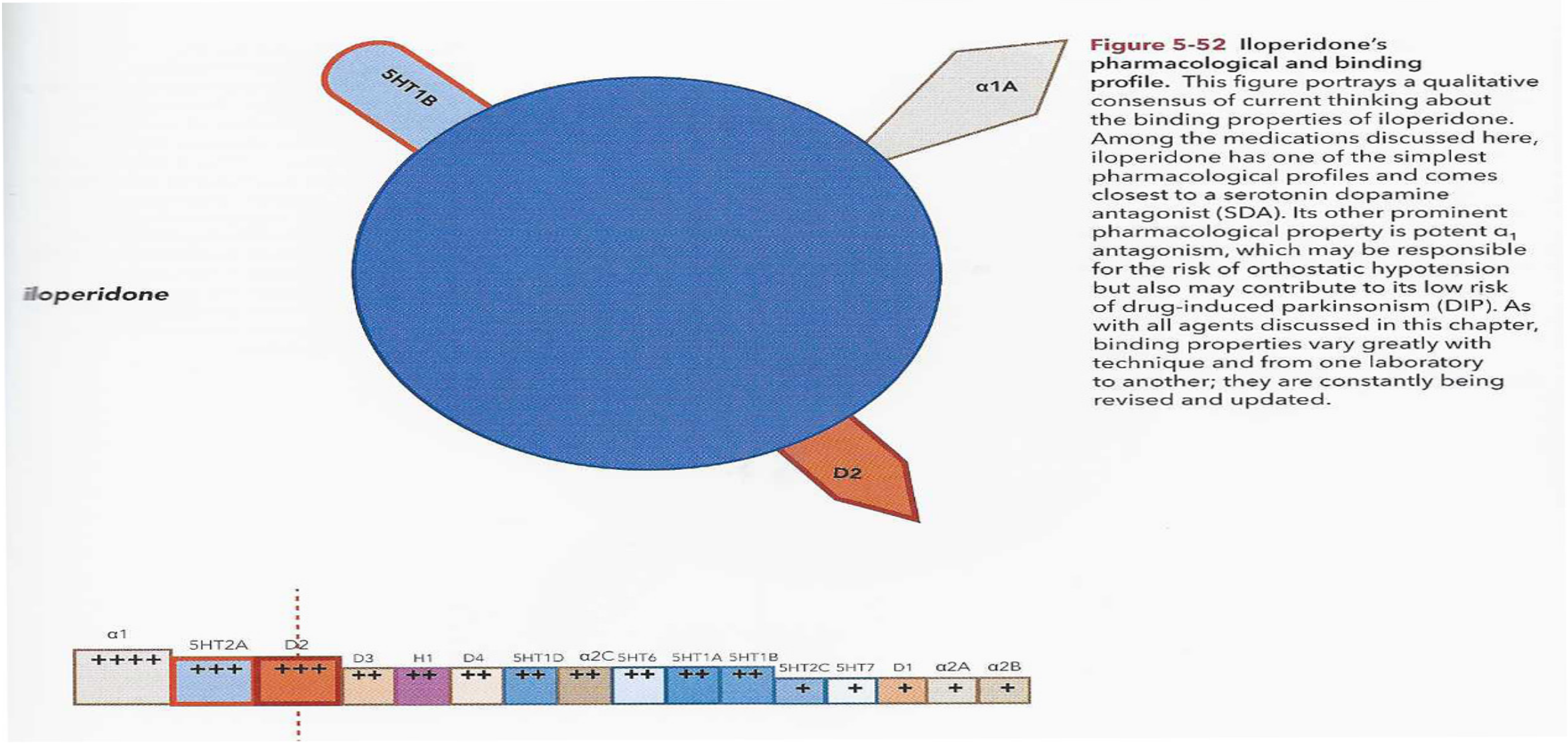


Figure 5-52 Iloperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of iloperidone. Among the medications discussed here, iloperidone has one of the simplest pharmacological profiles and comes closest to a serotonin dopamine antagonist (SDA). Its other prominent pharmacological property is potent α_1 antagonism, which may be responsible for the risk of orthostatic hypotension but also may contribute to its low risk of drug-induced parkinsonism (DIP). As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

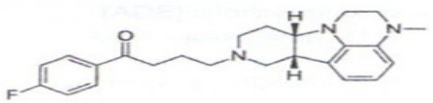
7. Lumateperoni (Caplypta)

7. Lumateperoni (Caplypta)

- glutamaatti
- risperidonin teho, ei EPS, uneliaisuus

Cafer, 2020

2020
$1300



Lumateperone (CAPLYTA)

LOO ma TE per one / kah PLY tah

"'Luminated Cap lighter"

- Antipsychotic (SGA)
- D2 antagonist - ⇩ DA
- 5-HT_{2A} antagonist - ⇧ DA
- Glutamate modulator

42 mg

FDA-approved for:
- Schizophrenia

Antipsychotics are represented with spooky mascots.

42 On Jackie Robinson Day (April 15), all players in Major League Baseball wear Robinson's uniform number, 42. For lumateperone, 42 mg is the only recommended dose.

Lumateperone is typically administered at night, which is also the time of day to illuminate a Jack-o'-lantern.

To improve tolerability, "take lumateperone with a bag of candy" (food) to delay peak blood levels.

Lumateperone (Caplyta) is a new antipsychotic that purportedly modulates glutamate in addition to the usual SGA mechanism of blocking D2 and 5-HT_{2A} receptors. However, the official prescribing information does not mention glutamate, suggesting the FDA saw insufficient evidence for lumateperone being a first-in-class novel antipsychotic. It appears to be equally effective as risperidone (Risperdal) with fewer side effects other than sedation (Citrome, 2016). Caplyta's effectiveness head-to-head with other antipsychotics is to be determined.

Lumateperone's D2 receptor occupancy is lower than most other antipsychotics. This means extrapyramidal side effects are unlikely. The other antipsychotics with low D2 occupancy are quetiapine (Seroquel) and clozapine (Clozaril).

Lumateperone is also a weak D2 receptor partial agonist. The stronger D2 partial agonists are aripiprazole (Abilify), brexpiprazole (Rexulti), and cariprazine (Vraylar).

Lumateperone has a favorable side effect profile. In clinical trials no single adverse effect led to > 2% discontinuation. The main side effects are somnolence/sedation (24% vs 10% placebo) and dry mouth (6% vs 2% placebo). At one year, lumateperone caused a modest weight loss of 3.2 kg (7 pounds) but a modest elevation in A1c and lipids. It does not appear to cause hypotension, prolactin elevation, or QT prolongation.

Lumateperone is extensively metabolized, resulting in more than twenty metabolites. Half-life is about 18 hours. It is a highly susceptible 3A4 substrate, making it contraindicated in combination with the medications listed below.

Because lumateperone can be highly sedating, it is typically administered at night. Taking lumateperone with food improves tolerability by delaying peak blood levels. This is more relevant if dosed during the day. Unlike ziprasidone (Geodon) and lurasidone (Latuda), taking lumateperone with food is not required for GI absorption.

Dosing: 42 mg is the only recommended dose, typically given at bedtime; Titration is not necessary (nor possible); No dose adjustment is required for renal impairment; Avoid with moderate/severe hepatic impairment.

Lumateperone is associated with a loss of 3.2 kg (7 pounds) at one year.

Lumateperone Pimavanseri

7. Lumateperoni (Caplypta)

Cafer, 2020

CYP 3A4!

Dynamic interactions:

- Antidopaminergic
- Extrapyramidal effects (mild)
- Sedation (high/moderate)
- Hypotensive effects (minimal)
- Prolactin elevation (minimal)

Kinetic Interactions:

- 3A4 substrate
- UGT substrate

The fish (our symbol for a 3A4 substrate) is big because with lumateperone 3A4 interactions are a very big deal.

Lumateperone is contraindicated with 3A4 inDucers due to rapid clearance. Levels will be decreased up to 20-fold, rendering lumateperone useless when given concomitantly with:

- Carbamazepine (Tegretol)
- Modafinil (Provigil)
- Phenytoin (Dilantin)
- Phenobarbital (Luminal)
- Oxcarbazepine (Trileptal)
- St. John's wort
- Rifampin (20-fold decrease)

20x

Lumateperone should also be avoided with moderate-to-strong 3A4 inHibitors which can dramatically increase blood levels. Strong 3A4 inhibitors include:

- Fluconazole and other -azole antifungals
- Clarithromycin (antibacterial)
- Ritonavir (antiretroviral, HIV treatment)

Lumateperone is a UGT substrate, which should not be combined with valproic acid (Depakote, Depakene)—a UGT inHibitor that dramatically increases lumateperone blood levels.

3A4 substrate (major)

UGT1A4 substrate

7. Lumateperoni (Caplypta)

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Metaboliakokeet
raskaustesti

Jacobson, 2023

Lumateperone

Screening laboratory tests	• LFTs (AST, ALT, total bilirubin) to determine general Child-Pugh classification (A—good hepatic function, B—moderately impaired hepatic function, and C—advanced hepatic dysfunction). Drug is not recommended for those with moderate to advanced hepatic dysfunction. • WBC count and differential. Preexisting leukopenia or neutropenia is a risk factor for a significant decline in WBC count or ANC values. If baseline values are low or the patient has a history of drug-induced leukopenia/neutropenia, obtain CBC with differential. • Fasting glucose, lipid profile, and weight for baseline values. • Pregnancy testing for patients of childbearing potential. Drug may cause extrapyramidal and/or withdrawal symptoms in neonates with third-trimester exposure.
Monitoring laboratory tests	• Obtain CBC with differential frequently during the first few months of therapy for patients with a low baseline WBC count or ANC or a history of drug-induced leukopenia/neutropenia. If ANC is $<1,000/mm^3$, discontinue drug and follow WBC count until recovery. • Periodic monitoring of metabolic parameters: fasting glucose, lipid profile, and weight. Drug is known to have a favorable metabolic profile compared to other antipsychotics, but labs are still recommended.

U.S. Food and Drug Administration: Caplyta (lumateperone) package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209500s005s006lbl.pdf. Accessed April 2022.

7. Lumateperoni (Caplypta)

Stahl, 2021

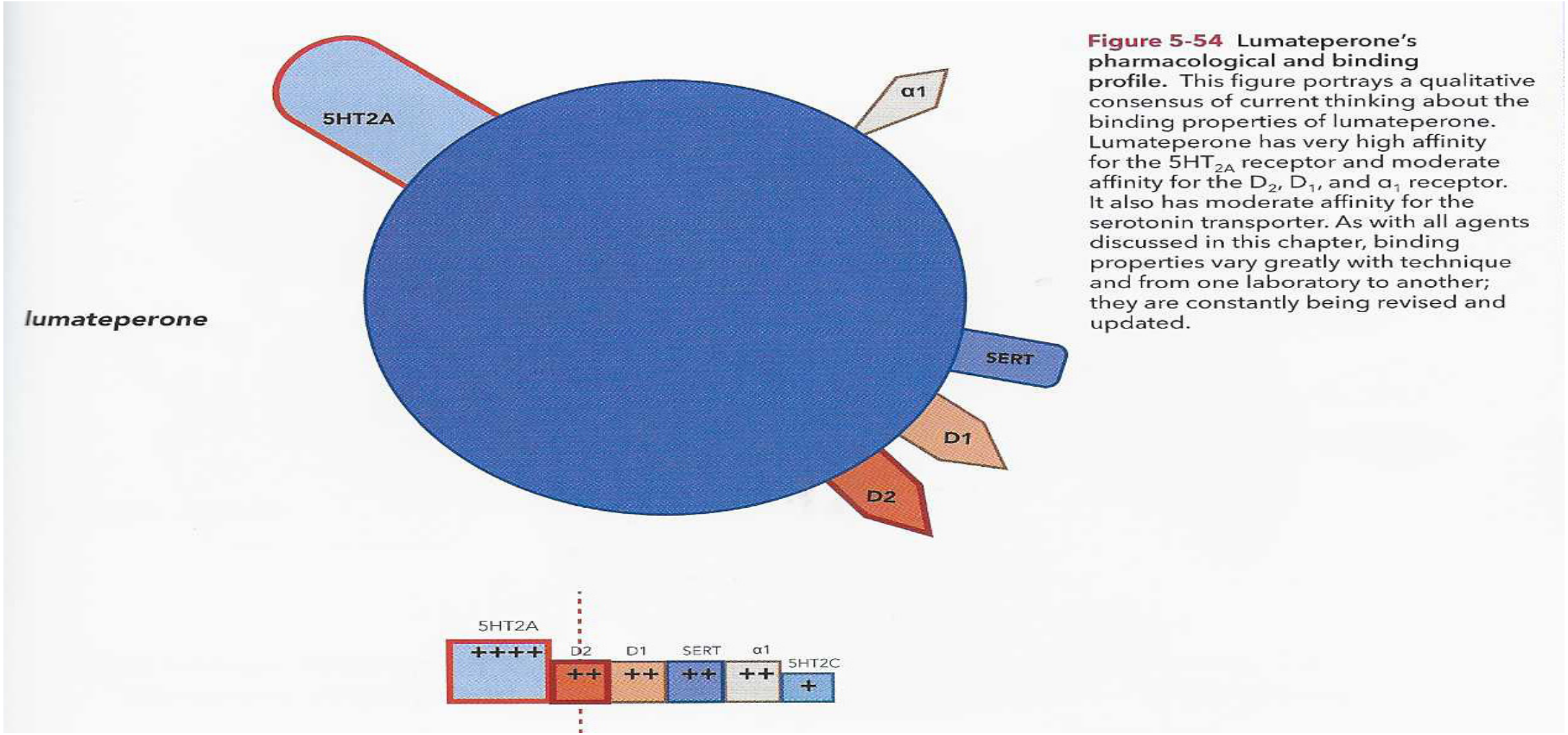

Figure 5-54 Lumateperone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of lumateperone. Lumateperone has very high affinity for the $5HT_{2A}$ receptor and moderate affinity for the D_2, D_1, and α_1 receptor. It also has moderate affinity for the serotonin transporter. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

8. Loksapiini (Loxapac, Loxitane)

8. Loksapiini(Loxapac, Loxitane)

LOXAPINE (Adasuve, Loxitane) Fact Sheet [G]

Bottom Line:
Loxapine is being rediscovered as a well-tolerated first-generation antipsychotic—it is of medium potency, and causes minimal EPS or weight gain. An oldy-but-goody alternative to atypical antipsychotics.

FDA Indications:
Schizophrenia; acute agitation associated with schizophrenia or acute bipolar mania.

Off-Label Uses:
Bipolar disorder; behavioral disturbances; impulse control disorders.

Dosage Forms:
- **Capsules (G):** 5 mg, 10 mg, 25 mg, 50 mg.
- **Single-use disposable inhaler (Adasuve)**, for acute agitation: 10 mg as inhalation powder.

Dosage Guidance:
- Schizophrenia: Start 10 mg BID; adjust to lowest effective dose. Dose range 60 mg–100 mg divided BID–TID; max FDA-approved dose is 250 mg/day, but doses >100 mg/day rarely used.
- Acute agitation (oral inhalation): Give 1 puff every 24 hours as needed (must be given by health care professional).

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: Capsule: $; inhalation: $$$

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8. Loksapiini(Loxapac, Loxitane)

Side Effects:

- Most common: EPS, headache, drowsiness, dry mouth, prolactin elevation (sexual side effects, amenorrhea, galactorrhea), throat irritation (Adasuve).
- Serious but rare: See class warnings in chapter introduction.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT2A receptor antagonist.
- Metabolized primarily by CYP2D6 and 3A4; t ½: 4–8 hours.
- Caution with inhibitors of CYP2D6 and 3A4 and inducers of 3A4; adjust dose.

Clinical Pearls:

- Loxapine is an intermediate-potency conventional (typical) antipsychotic; this leads to less EPS compared to high-potency agents (eg, haloperidol, fluphenazine) and to less sedation, less orthostasis, and fewer anticholinergic side effects compared to low-potency agents (eg, chlorpromazine).
- Loxapine belongs to the dibenzoxazepine class of antipsychotics and is structurally related to clozapine (which belongs to the chemically akin class of dibenzodiazepines). Some have argued that loxapine may behave as an atypical antipsychotic.
- The newer Adasuve oral inhalation version has the advantage of treating agitation quickly without the need for swallowing or a shot. But the risks of bronchospasm and respiratory arrest, along with the contraindication in patients with asthma, COPD, or other lung disease, make this formulation rather unappealing overall.

Fun Fact:

Loxapine is metabolized to the tetracyclic antidepressant amoxapine.

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050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

9. Amisulpiridi (Solian)

9. Amisulpiridi (Solian)

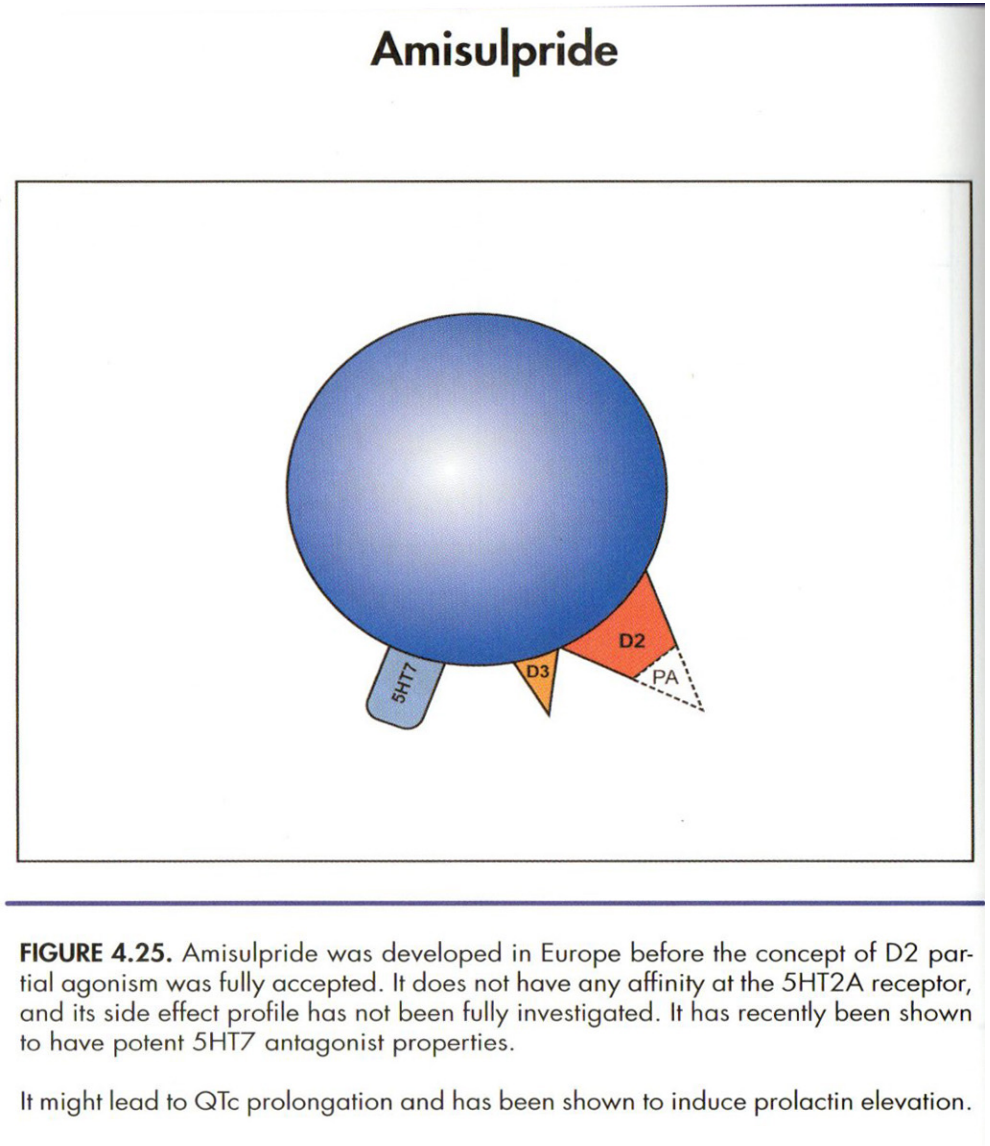

FIGURE 4.25. Amisulpride was developed in Europe before the concept of D2 partial agonism was fully accepted. It does not have any affinity at the 5HT2A receptor, and its side effect profile has not been fully investigated. It has recently been shown to have potent 5HT7 antagonist properties.

It might lead to QTc prolongation and has been shown to induce prolactin elevation.

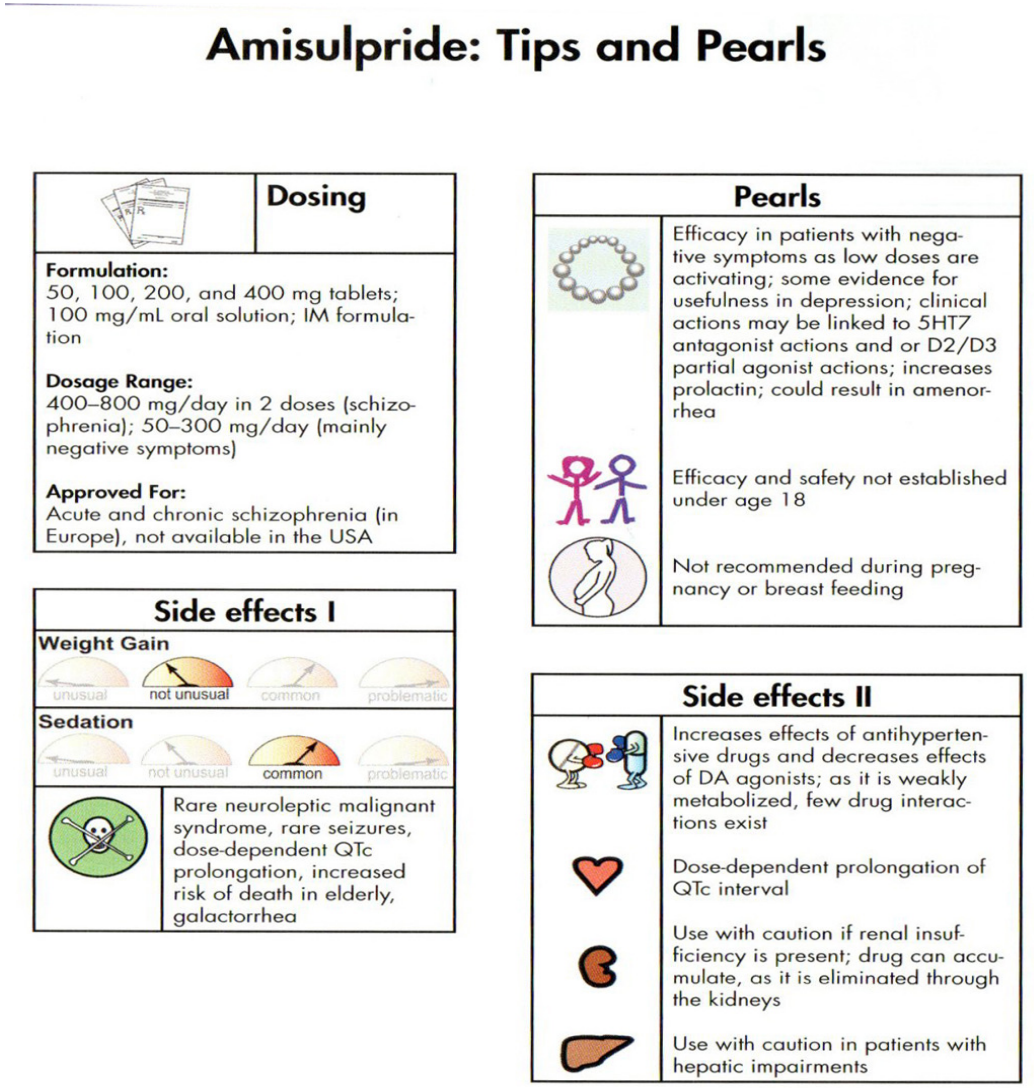

FIGURE 4.26. Dosing and interaction information for amisulpride.

Stahl and Mignon 2010

9. Amisulpiridi (Solian)

Stahl, 2021

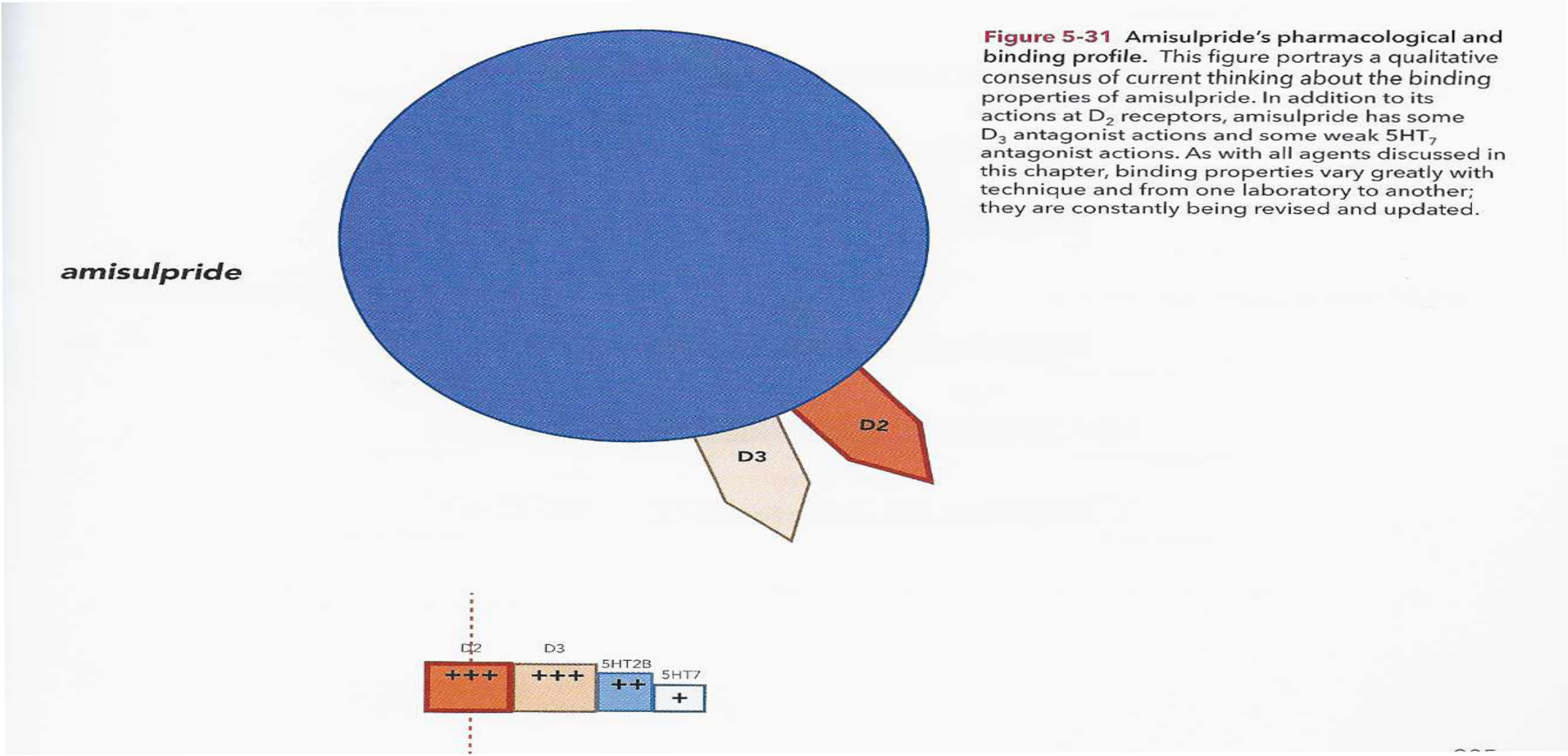

Figure 5-31 Amisulpride's pharmacological and binding profile. *This figure portrays a qualitative consensus of current thinking about the binding properties of amisulpride. In addition to its actions at D_2 receptors, amisulpride has some D_3 antagonist actions and some weak $5HT_7$ antagonist actions. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.*

050923 Uudet psykoosilääkkeet - yleistä lääkkeistä joilla on antipsykoottista tehoa

10. Molindoni(Moban)

10. Molindoni(Moban)

MOLINDONE (Moban) Fact Sheet [G]

Bottom Line:
Molindone is an effective, well-tolerated first-generation antipsychotic of medium potency—a solid medication that some clinicians have gained experience with and favor for select patients. Recently it has been reintroduced into the market, and is still generic and inexpensive.

FDA Indications:
Schizophrenia.

Off-Label Uses:
Bipolar disorder; behavioral disturbances; impulse control disorders.

Dosage Forms:
Tablets: 5 mg, 10 mg, 25 mg.

Dosage Guidance:
Start 50 mg–75 mg/day divided BID–QID; increase to 100 mg/day in 3 or 4 days. Max dose 225 mg/day divided TID–QID.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $

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10. Molindoni(Moban)

Side Effects:

- Most common: Sedation (dose-related), EPS, agitation.
- Serious but rare: Rare reports of leukopenia and leukocytosis.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 antagonist.
- Metabolized primarily through CYP450; t ½: 1.5 hours.

Clinical Pearls:

1. Asenapiini (Sycrest)

- Molindone is an intermediate-potency conventional (typical) antipsychotic; this leads to less EPS compared to high-potency agents (eg, haloperidol, fluphenazine) and to less sedation, less orthostasis, and fewer anticholinergic side effects compared to low-potency agents (eg, chlorpromazine).
- Unlike most antipsychotics, molindone has been shown to reduce weight in some patients.

Fun Fact:

In 2010, the only manufacturer of molindone in the US (as brand Moban), Endo Pharmaceuticals, announced that they would be discontinuing production because of poor sales. In December 2015, Core Pharma launched a new generic version, bringing molindone back to life.

Puzantian T and Carlat D, 2020

11. Muita uusia lääkkeitä joilla antipsykoottista tehoa

Vanhoja ja uusia kehitteillä

11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- tsotepiini

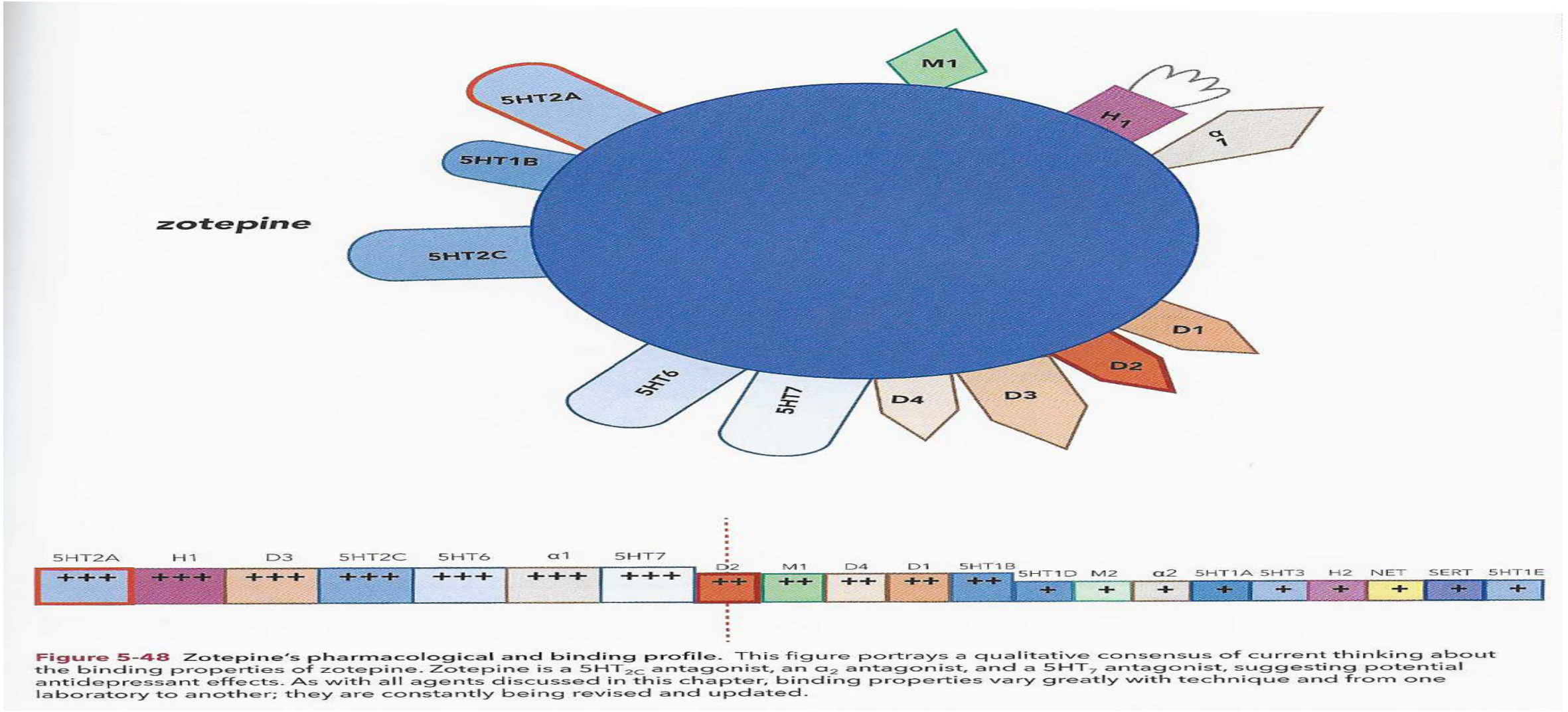

Figure 5-48 Zotepine's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of zotepine. Zotepine is a $5HT_{2C}$ antagonist, an α_2 antagonist, and a $5HT_7$ antagonist, suggesting potential antidepressant effects. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

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11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- perospironi

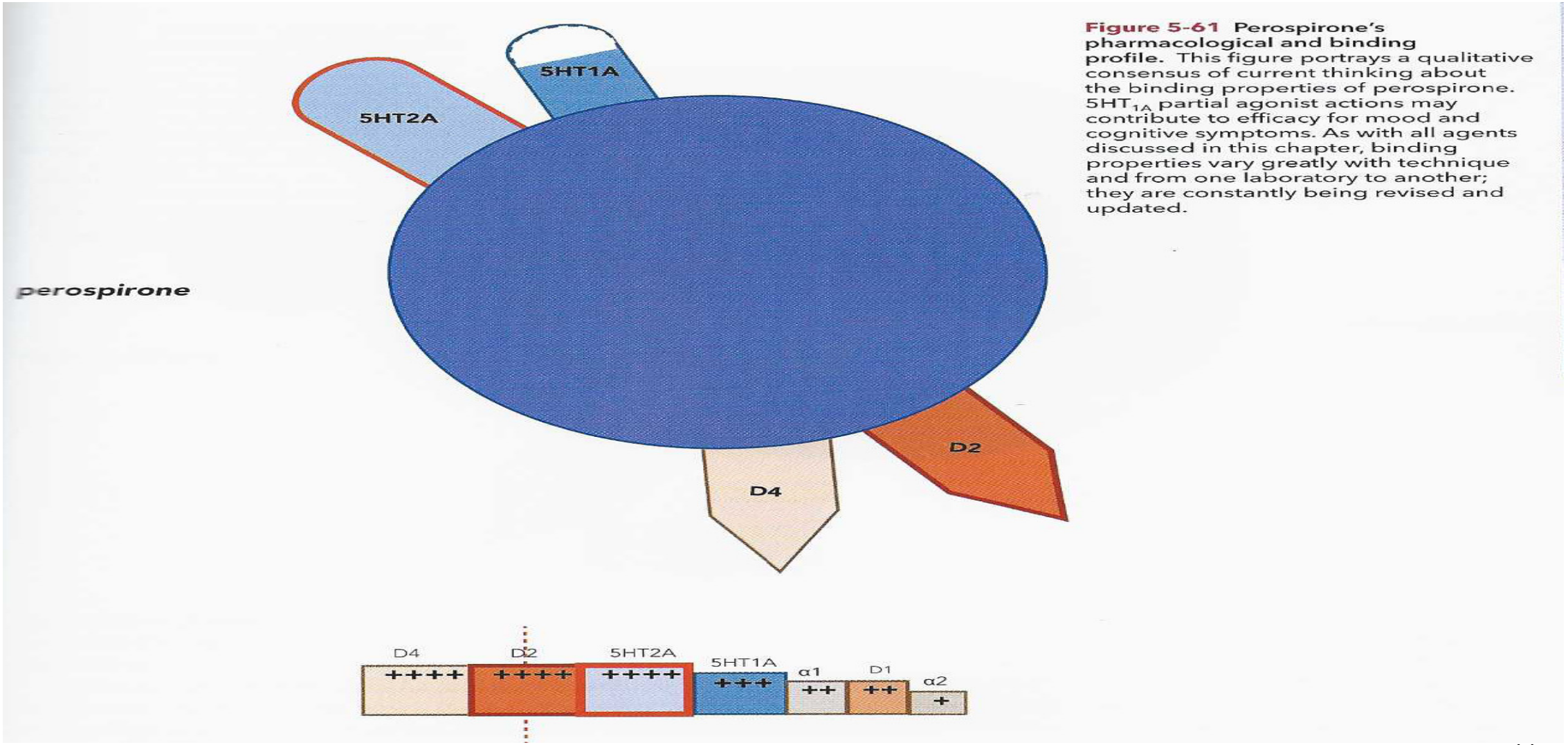

Figure 5-61 Perospirone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of perospirone. $5HT_{1A}$ partial agonist actions may contribute to efficacy for mood and cognitive symptoms. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

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11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- bionanseriini

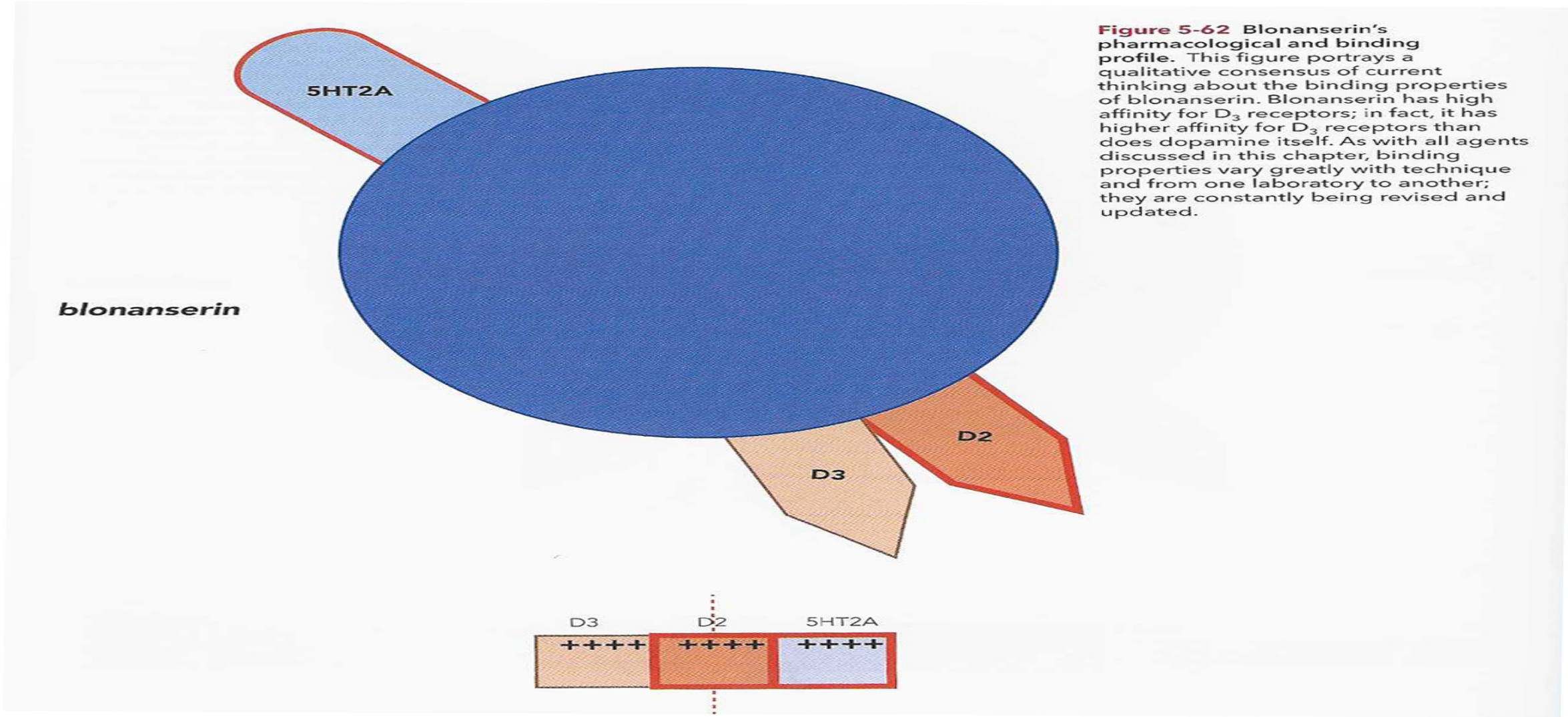

Figure 5-62 Blonanserin's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of blonanserin. Blonanserin has high affinity for D_3 receptors; in fact, it has higher affinity for D_3 receptors than does dopamine itself. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Stahl, 2021

11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- roluperidoni

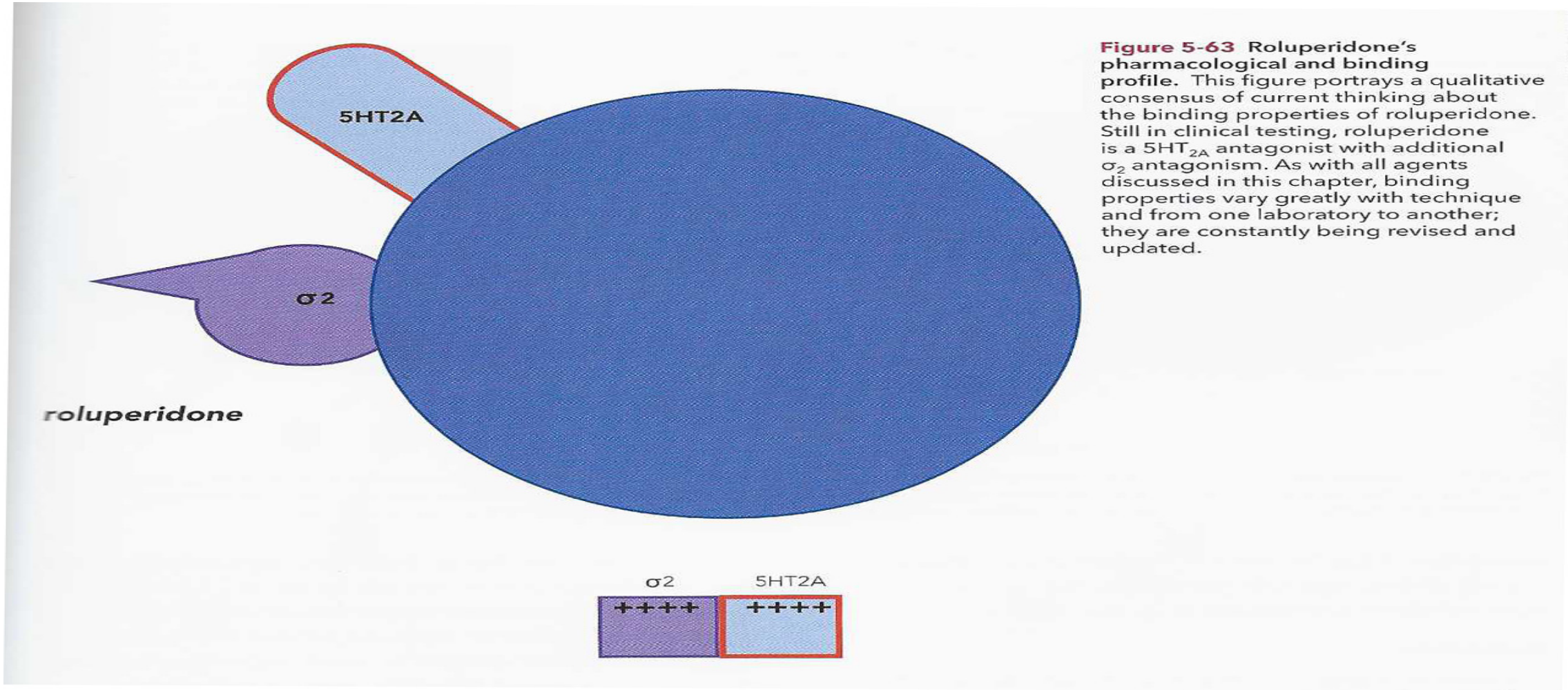

Figure 5-63 Roluperidone's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of roluperidone. Still in clinical testing, roluperidone is a $5HT_{2A}$ antagonist with additional σ_2 antagonism. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Stahl, 2021

11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- ksanomeliini

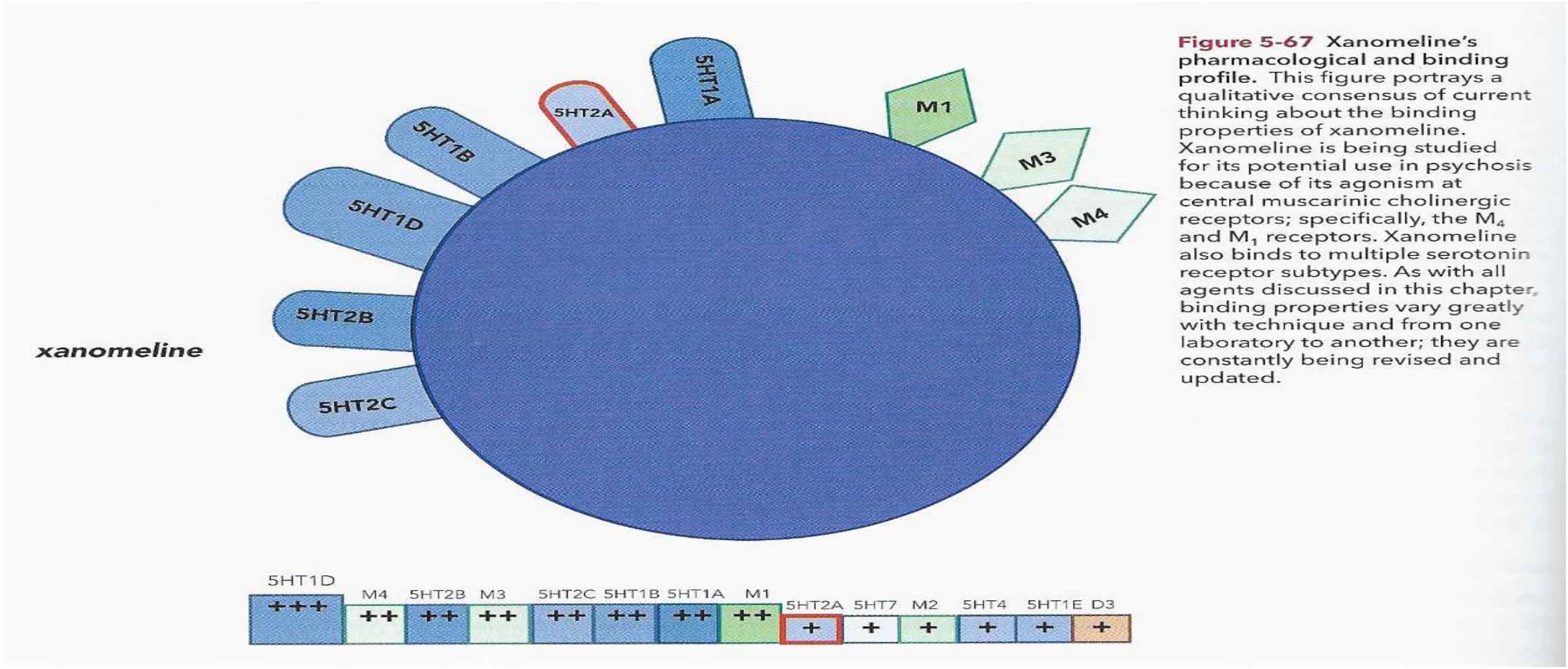

Figure 5-67 Xanomeline's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of xanomeline. Xanomeline is being studied for its potential use in psychosis because of its agonism at central muscarinic cholinergic receptors; specifically, the M_4 and M_1 receptors. Xanomeline also binds to multiple serotonin receptor subtypes. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

Stahl, 2021

11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- TAAR-mekanismi

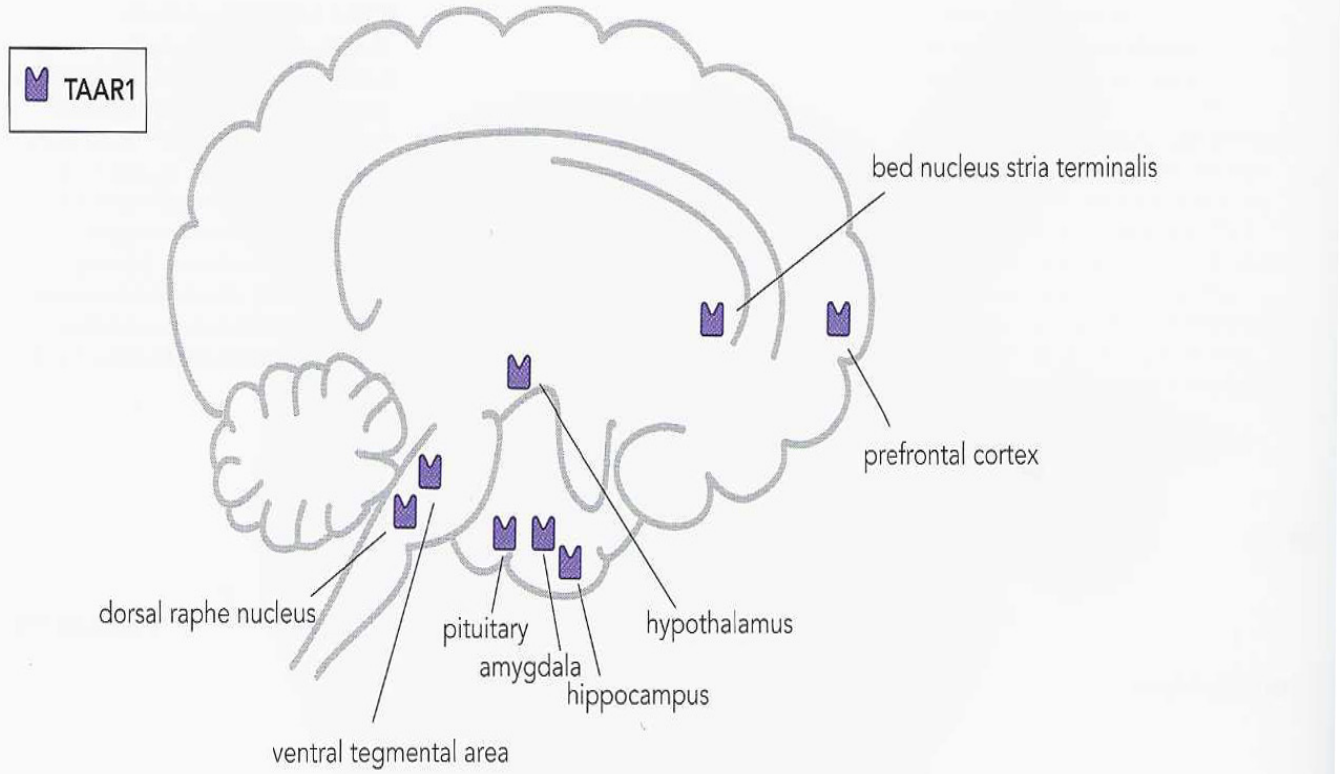

Figure 5-64 Localization of trace amine-associated receptor type 1 (TAAR1). A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). TAAR1 is widely expressed throughout the brain, including in monoamine brainstem centers (dorsal raphe nucleus, ventral tegmental area) and in monoamine projection areas.

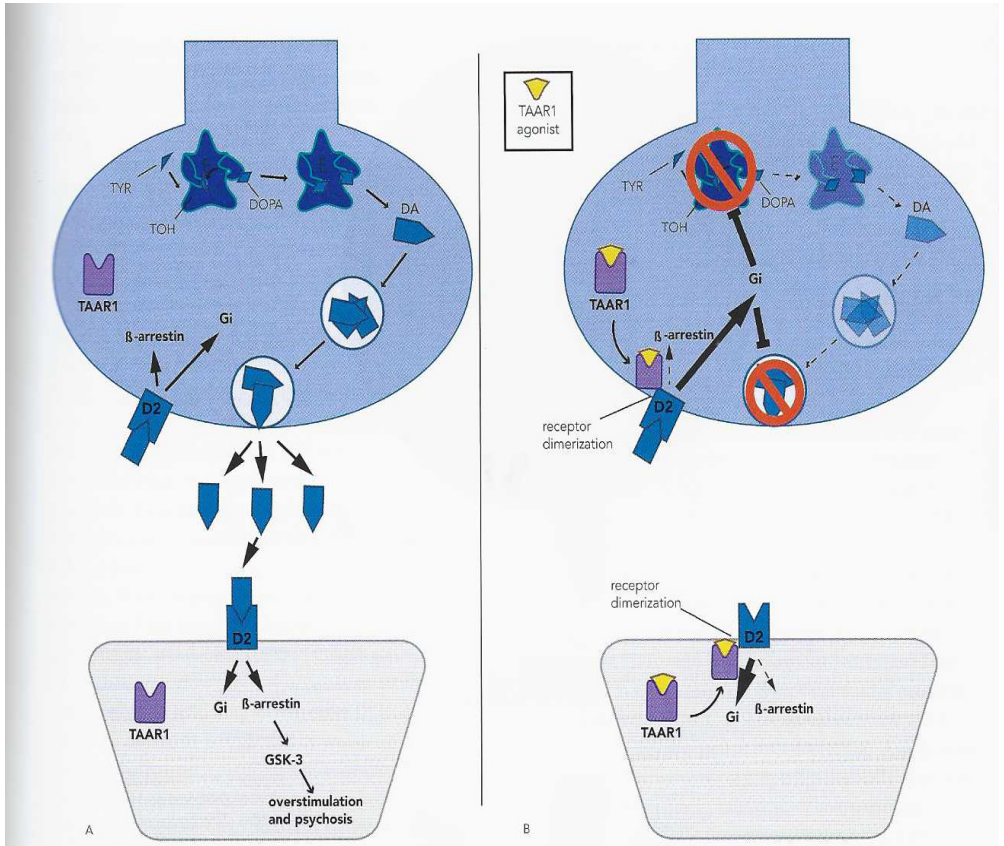

Figure 5-65 Agonism of trace amine-associated receptor type 1 (TAAR1). Trace amines are formed from amino acids when either the tyrosine hydroxylase (TYR) step or the tryptophan hydroxylase (TOH) step is omitted during production of dopamine or serotonin, respectively. (A) Dopamine is produced and packaged into synaptic vesicles, then released into the synapse. Dopamine binding at both pre- and postsynaptic D_2 receptors can either trigger the inhibitory G (Gi) protein signal transduction cascade or the β-arrestin 2 signal transduction cascade. The β-arrestin 2 cascade leads to production of glycogen synthase kinase 3 (GSK-3); too much GSK-3 activation may be associated with mania or psychosis. (B) When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with D_2 receptors (heterodimerization). This biases the D_2 receptor toward activating the Gi signal transduction cascade instead of the β-arrestin cascade. Presynaptically, amplification of the Gi pathway leads to inhibition of the synthesis and release of dopamine, which would be beneficial in cases of psychosis. Postsynaptically, amplification of the Gi pathway can lead to reduced production of GSK-3.

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11. Muita uusia lääkkeitä joilla antipsykoottista tehoa- SEP-363856

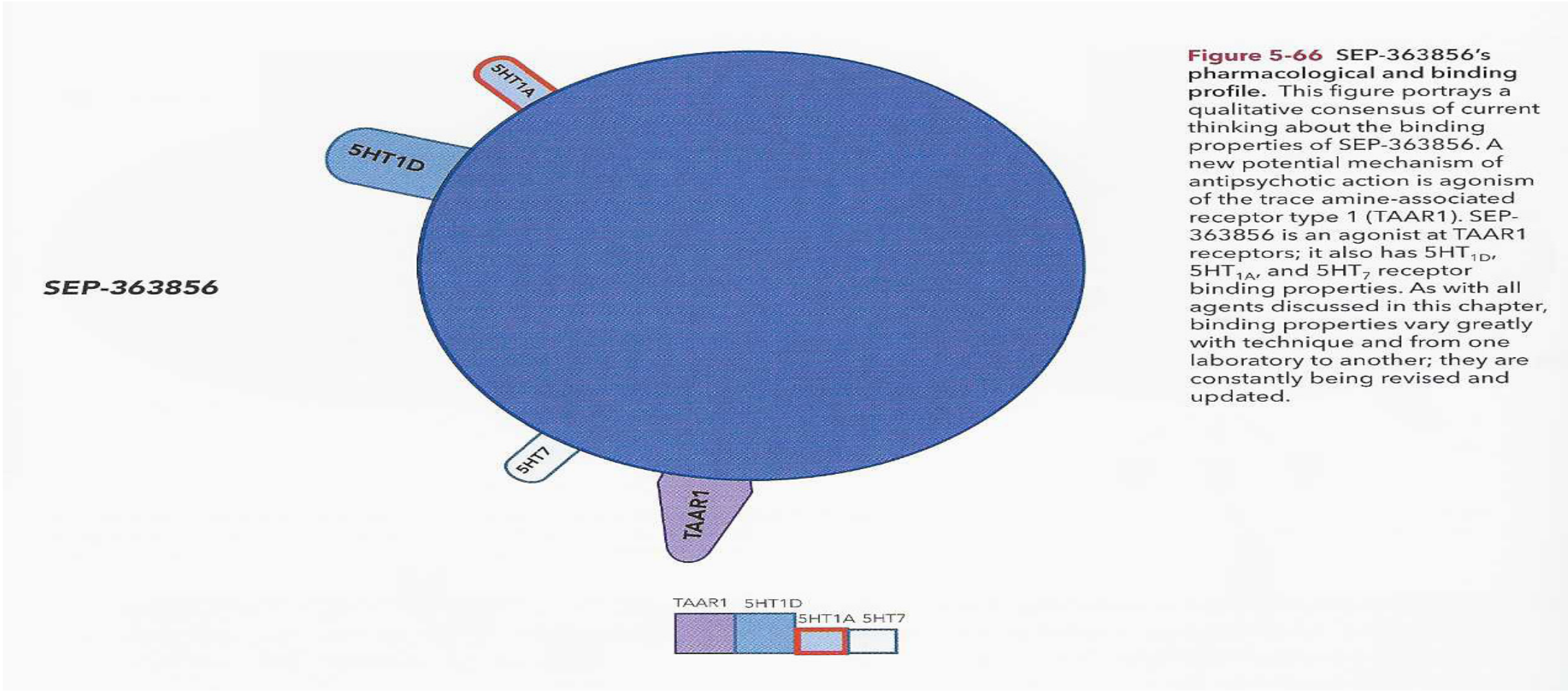

Figure 5-66 SEP-363856's pharmacological and binding profile. This figure portrays a qualitative consensus of current thinking about the binding properties of SEP-363856. A new potential mechanism of antipsychotic action is agonism of the trace amine-associated receptor type 1 (TAAR1). SEP-363856 is an agonist at TAAR1 receptors; it also has $5HT_{1D}$, $5HT_{1A}$, and $5HT_7$ receptor binding properties. As with all agents discussed in this chapter, binding properties vary greatly with technique and from one laboratory to another; they are constantly being revised and updated.

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