Welcome to today's Insight APSAD webinar.

We'll be starting a little after 10am (QLD time).

- Use the chat icon for all questions and comments – *select All panelists and attendees.*
- If you are on a computer and Zoom enters full screen mode – you can press the escape button or visit "View Options" at the top of the screen to change the layout.
- If you are experiencing other problems or require further technical assistance call Zoom on **1800 768 027** – the webinar ID is **753-782-670.**
- A pdf version of today's presentation will be available soon in the chat window.
- A recording of this webinar will be available on our YouTube channel in the coming weeks.

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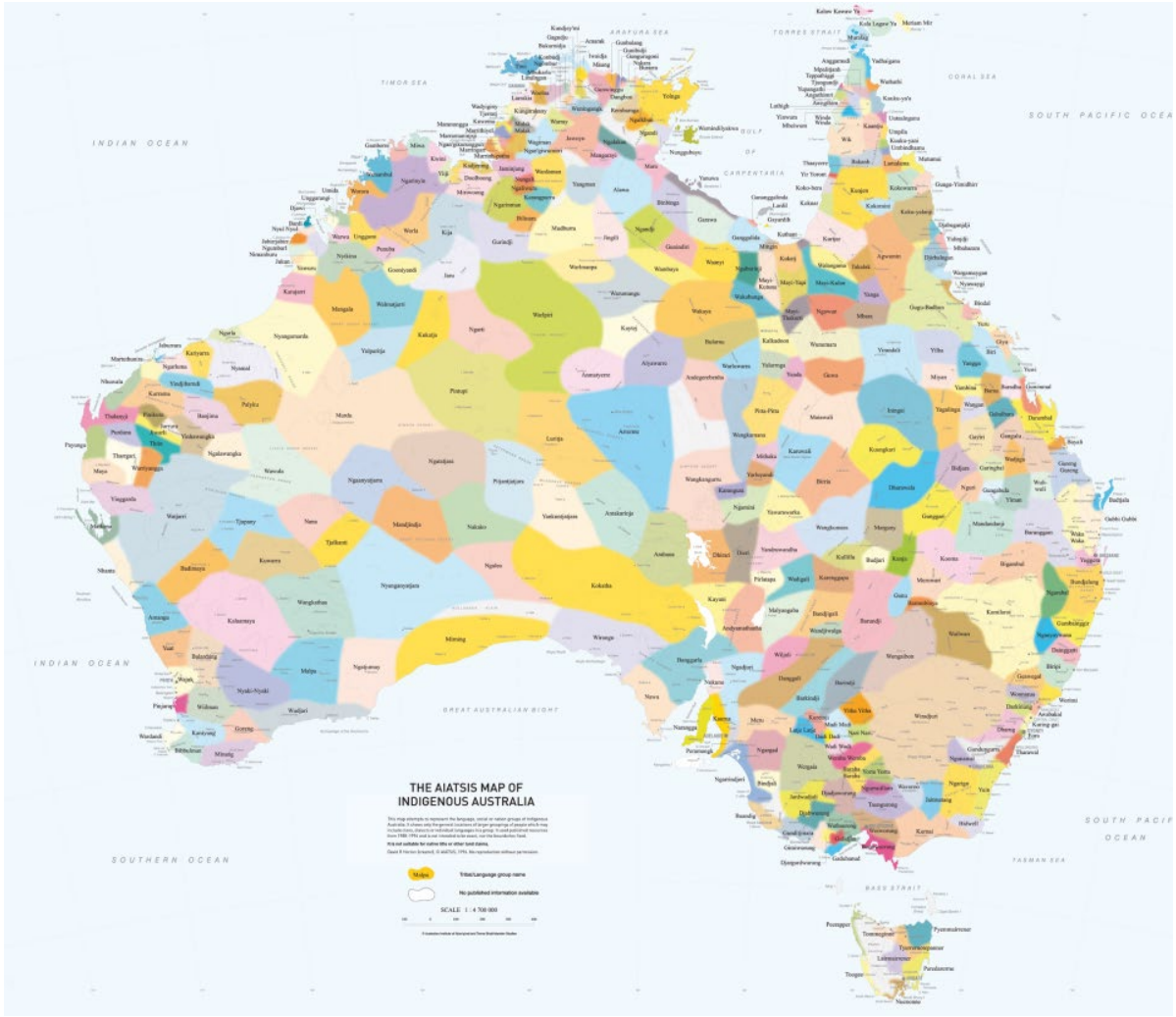
The Australasian Professional Society on Alcohol and other Drugs



We acknowledge the Traditional Owners of the land on which this event takes place and pay respect to Elders past, present and future.

This map attempts to represent the language, social or nation groups of Aboriginal Australia. It shows only the general locations of larger groupings of people which may include clans, dialects or individual languages in a group. It used published resources from 1988-1994 and is not intended to be exact, nor the boundaries fixed. It is not suitable for native title or other land claims. David R Horton (creator), © AIATSIS, 1996. No reproduction without permission. To purchase a print version visit: www.aiatsis.ashop.com.au/

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Quetiapine and substance use

Helpful or hazardous?

Anita Myers

Disclaimer: This content has been developed out of the work done for real-time reporting project. It is primarily based off literature evidence.

Any clinical support contact your local clinical advisory service – Queensland ADCAS 1800 290 928

What is quetiapine?

A widely used atypical, or second-generation antipsychotic. [1-3]

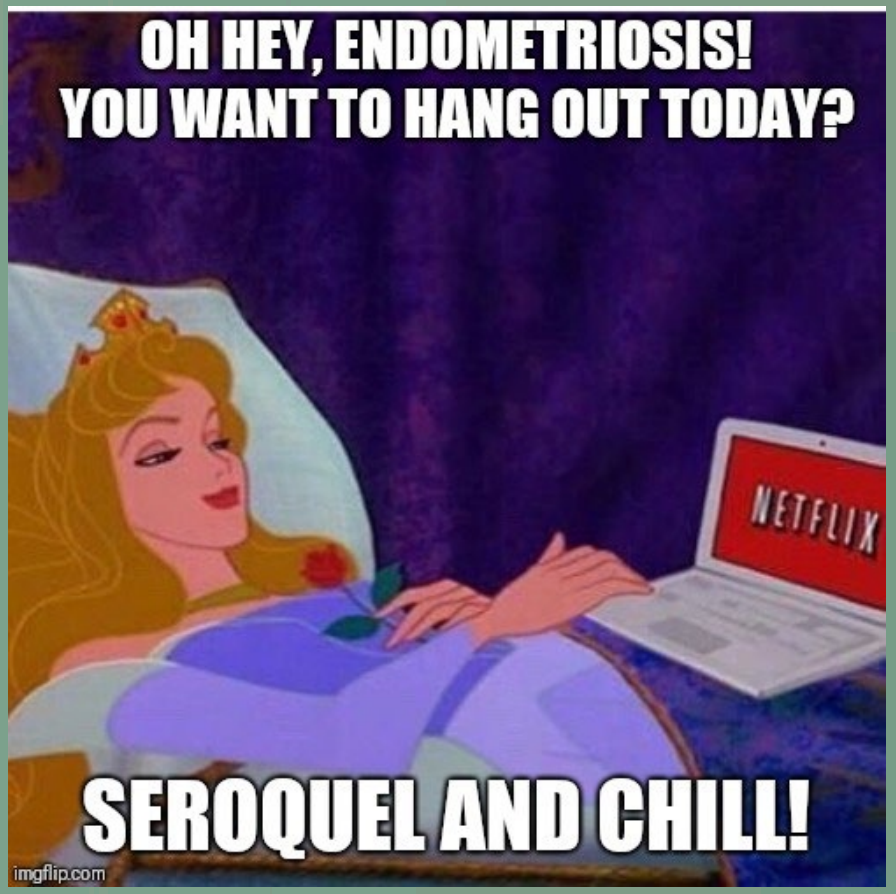
Available in two forms:

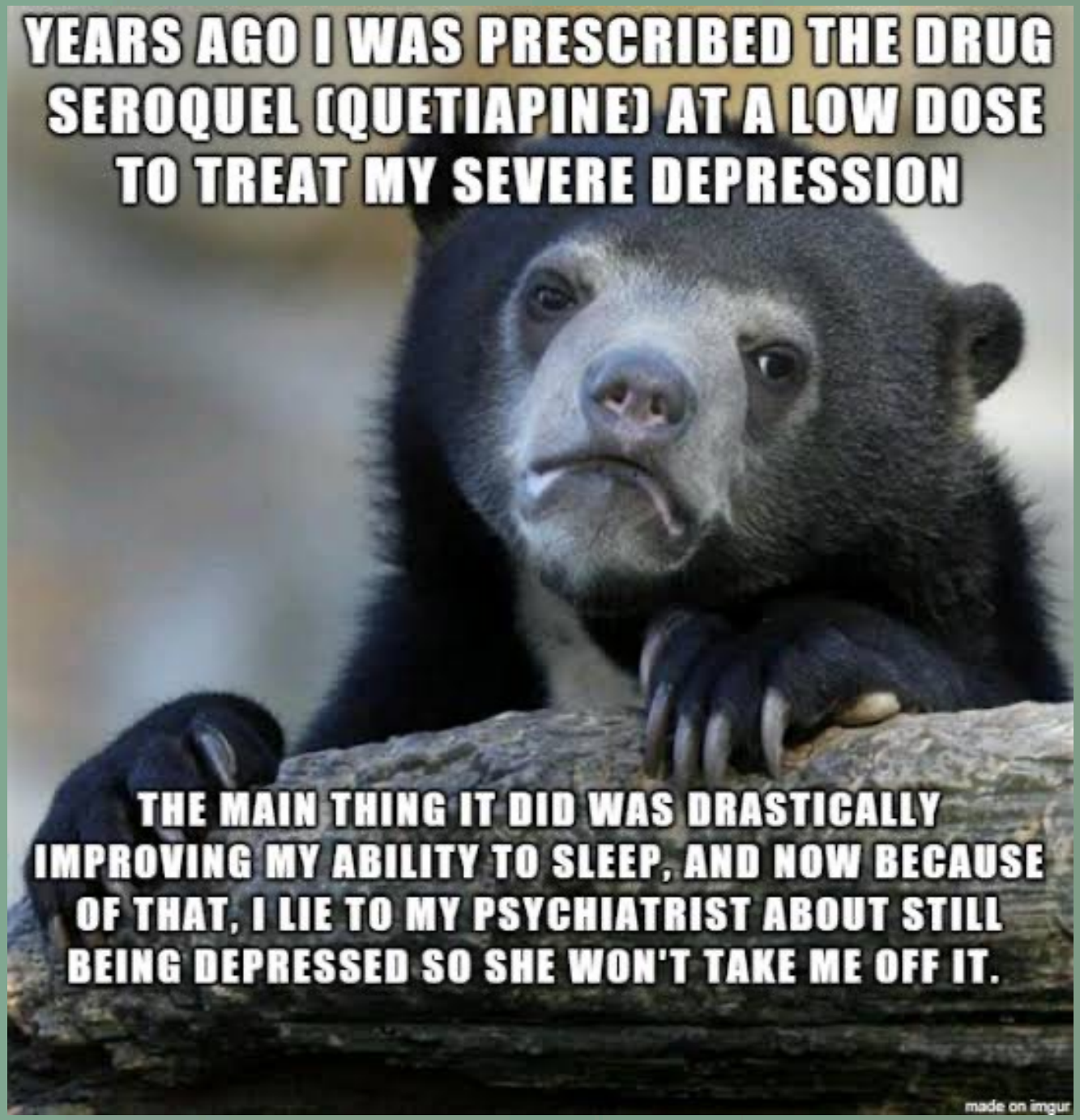
- Immediate release
- Extended release


WHEN THE
SEROQUEL HITS


Skipping a dose of seroquel be like
OH BOY 3 AM


SEROQUEL!
SEROQUEL FOR EVERYONE!


OH HEY, ENDOMETRIOSIS!
YOU WANT TO HANG OUT TODAY?
NETFLIX
SEROQUEL AND CHILL!
imgflip.com

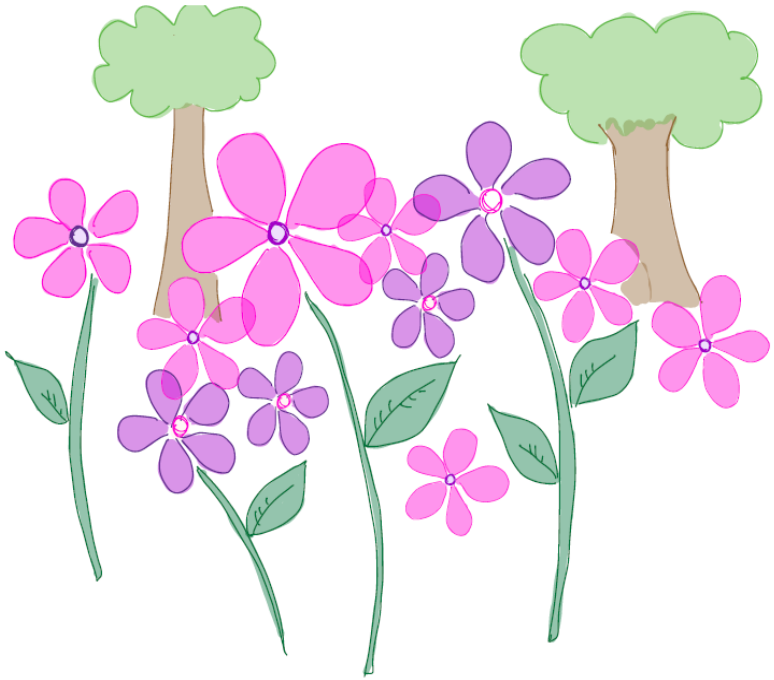

YEARS AGO I WAS PRESCRIBED THE DRUG SEROQUEL (QUETIAPINE) AT A LOW DOSE TO TREAT MY SEVERE DEPRESSION
THE MAIN THING IT DID WAS DRASTICALLY IMPROVING MY ABILITY TO SLEEP, AND NOW BECAUSE OF THAT, I LIE TO MY PSYCHIATRIST ABOUT STILL BEING DEPRESSED SO SHE WON'T TAKE ME OFF IT.
made on imgur

History of quetiapine?

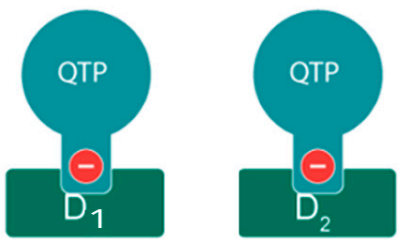
- Dibenzothiazepine derivative[4]
- First registered in 1997[5]
- Developed to provide relief from mental illness whilst eliminate all extrapyramidal side effects[5] that were common in many of the first generation antipsychotics[6]

How does it work?

- Like most psychotropic medication – the exact mechanism remains poorly understood! [7]



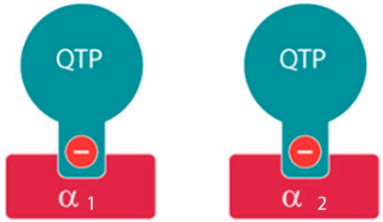
How does it work? [8,9]



dopamine D_1/D_2 antagonist

H_1 histamine antagonist

potent 5-HT_{2A} antagonist



α_1 / α_2 adrenoreceptor antagonist

partial 5-HT_{1A} agonist

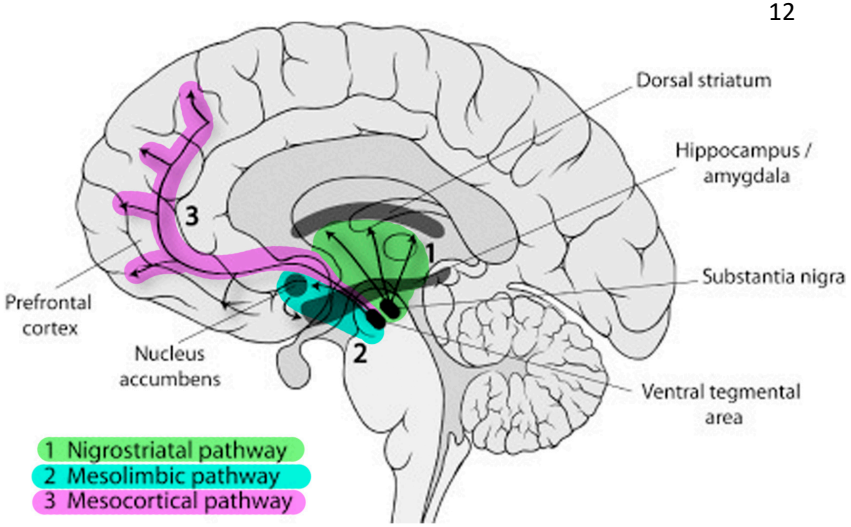
σ_1 receptor agonist

How does it work? - dopamine [8,9]

- Reduction of the dopamine transition is believed to improve psychotic symptoms and is explained by the dopamine hypothesis

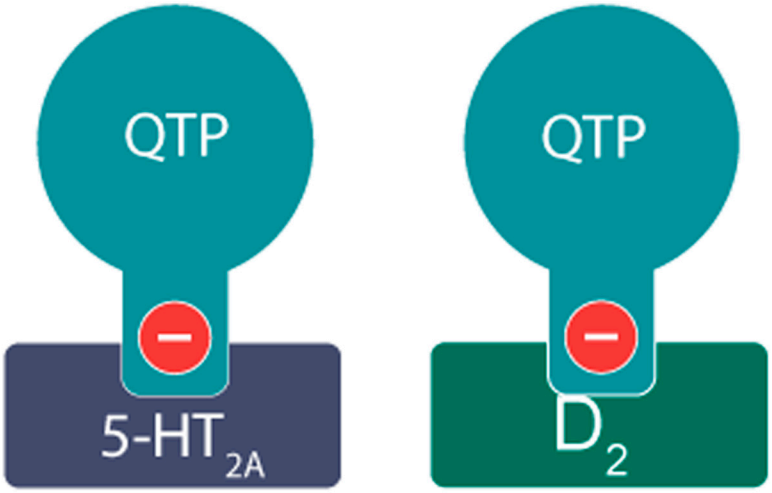
- Increase activity of dopamine (particularly the mesocortical and mesolimbic pathways[10]) is associated with symptoms of schizophrenia[11]

12



How does it work? - $5HT_{2A}$ antagonism[13]

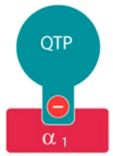
- $5HT_{2A}$ antagonism stimulates dopamine release in a range of pathways
- reduces the side effects of a typical dopamine blocker
- The ratio of dopamine: $5HT_{2A}$ results in the medication being classed as “atypical”



How does it work?

- Partial 5-HT_{1A} agonism – responsible for antidepressant and anxiolytic effects[13]

- H_1 antagonist – hypnotic, sedative and appetite promoting effects[14]



- α_1 antagonist – theoretically increases dopamine in the striatum and decreased EPSE, [15] anxiolytic effects[16]

- α_2 antagonist – mediates dopamine release in pre-frontal cortex – improving cognition[17]

- σ1 agonists – least understood[18] through multiple neurotransmission pathways (including glutamatergic, cholinergic and serotonergic transmissions) – Antidepressant.[19]

How does it work? - Metabolites

Norquetiapine (major active metabolite) – affinity to $5HT_{1A}$ receptor (leading to antidepressant effects) and to acetylcholine receptors – leading to anticholinergic effects[2, 3, 21, 22]

More information on different neurotransmitters can be found from Insight youtube channel

Neurotransmitters

Insight Queensland • 368 views • 6 months ago

This video is for clinicians to give a brief overview of the key neurotransmitters identified in common substances used and their action. The information contained within this video was taken from:...

CC

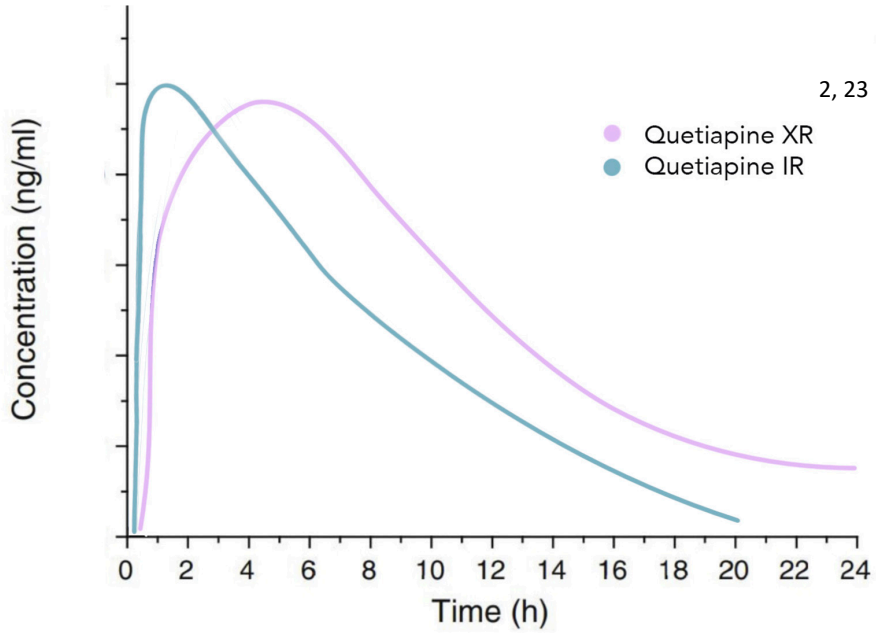
How does it work? – Dose effects[17]

- **25mg** - a H_1 receptor and α_1 adrenrgic receptor antagonist – sedative and anxylotic effects
- **50-200mg** – antagonizing serotonin receptors (5HT) – antidepressant effects
- **>300mg** - antagonises dopamine receptors - antipsychotic effects

Pharmacokinetics

- Metabolised by P450 system (CYP3A4 + lesser extent CYP2D6 and CYP2C9)[21, 22]
- Major metabolite – norquetiapine (N-Desalkylquetiapine)[21, 22]

- IR formulations reach maximum plasma concentration 1 hour post ingestion [2]
- XR Formulations have peak plasma after 6 hours.[3]
- Elimination half-life of quetiapine is 7 hours and 12 hours for norquetiapine.[2, 3]
- XR formulations appear to reach lower peak plasma concentrations and have less sedative effects.[23]



Concentrations will be affected by other medications/ substances that are metabolised by the same systems it is metabolised with - particularly CYP3A4 (*things like azole antifungals and PPIs). [2, 3]

Quetiapine like many other antipsychotic drugs were generally considered to be devoid of abuse potential[8]

The growth of prescribing quetiapine

- Rapid increase in prescription rates – latest Australian PBS data (2015) – 285-fold increase in prescribing since 2000[24, 25]
- Most increase low-dose (between 25-100mg[26]) Immediate release (IR) versions – believed to be for off-label indications[5]
- In 2010 the manufacturer had to pay US$250 million following government allegations of misconduct around its promotion of off-label use[27]
- Little effect on off-label prescribing rates with estimated 60-70% of patients treated in the US being prescribed for off-label use [5, 28]

Why is this a problem??

Much of the misuse and non-prescribed quetiapine use comes from diversion[7, 8] – the easier it is to get – the easier it is to divert!

What is it used for?

TGA approval[1-3]

- Quetiapine immediate release - Bipolar affective disorder (including treatment for manic and depressive episodes) and treatment for schizophrenia

- Quetiapine extended release - approved for the same as immediate release but also for the treatment of major depressive disorder (MDD) who are either unable to, or have had a poor response to alternative therapies and the treatment of generalized anxiety disorder (GAD)

Recommended maximum dosage 800mg[8, 29]

What is it used off-label for? [8, 21, 30-32]

- Insomnia (generally low doses <100mg)
- For other anxiety disorders (including, but not limited to, OCD and PTSD)
- ADHD (for side effects)
- Psychosis and behavioural disturbances in dementia
- Psychosis in Parkinson's disease
- Eating disorders
- Borderline personality disorder

Quetiapine and Sleep

One of the major driving forces behind increased quetiapine prescriptions is its use as a hypnotic.[5, 8, 26] - arguably due to concerns about prescribing benzodiazepines.

- About 1 in every 3 people (Number needed to harm – NNH 3) experience sedation[32]
- Lack of evidence of efficacy and safety to support its use for insomnia[33-35]
- Cases of dose escalation to maintain effect[36]
- Australian guidelines for insomnia advise against use of antipsychotics for the management of insomnia[35, 37]

How is it used in substance use?

The increased dopamine in the pre-frontal cortex, coupled with hypnotic and anxiolytic properties has resulted in quetiapine being used off-label for the treatment for substance use disorders both to aid in withdrawal and maintaining abstinence[7, 30, 38-43]

Evidence presented on its efficacy are based off the published evidence.

Results were from a number of small studies – both in patients with and without co-morbid mental health conditions – with patients with comorbid conditions generally having the greatest improvements[44]

How is it used in substance use?

Alcohol Use Disorder

- Decreased alcohol intake[39, 45]
- Reduced craving, increase sedation and improving sleep, and reducing anxiety[39, 46, 47]
- Results maintained even in cases of continued alcohol use[48]
- Positive results were not universal in all studies[49]

Alcohol withdrawal

- Reduction in some withdrawal symptoms in animal studies[50]
- Doesn't seem to have the same seizure-threshold reduction like other antipsychotics[51]

How is it used in substance use?

Opioid Withdrawal

Used for opioid detoxification to reduce anxiety, pain and cravings[40, 52]

Used as an adjunct for assisting with persistent pain during an opioid detox.[53]

Cannabis use disorder

Reduced use[54-56] – not specific about what lead to that.

How is it used in substance use?

Amphetamine(s) Use disorder

- Improvement in depression, sleep and cognitive function (even in ongoing use)[57]
- Animal studies that show improvement in methamphetamine-induced cognitive deficits[58]

Cocaine use disorder

- Decreased craving and reduction in use[59] (although not consistent[60])

How is it used in substance use?

Polysubstance

- Used to decrease anxiety, insomnia, agitation and obsessional symptoms[60]

Benzodiazepines

- couldn't find direct evidence for its use for benzodiazepine use disorder, although theoretically its sedative and anxiolytic properties would indicate that it would be useful.

How is it used in substance use – Non-prescribed use

Quetiapine – quell, Susie Q, baby heroin, snooze berries, squirrel[8] "getting snowed"

Routes of administration [8, 25, 62]

- Oral (high doses)
- Insufflation (snorting)
- IV
- Smoking
- Case reports of rectal administration

How is it used in substance use – Non-prescribed use

Highest use in incarcerated populations and those who use substance (often in context of polysubstance use) [7, 8]

Difficult to estimate numbers[62, 63]

- IRDS - ~9% of injecting drug users
- ERDS -~ 7% of other substance users

using non-prescribed antipsychotic medication (~60% of SGA antipsychotics were quetiapine[64])

There was evidence that it there was common misuse amongst methadone maintence[65]

Dose

Difficult to tell! – up to and over 2000mg case reports[9, 66]

Bluelight doses between 25mg (to come off stimulants) – 1400mg

How is it used in substance use – Non-prescribed use

Reasons used

To get "high" or also to assist with a "downer" to mediate the effects of stimulants[8]
Primarily used for self-medication rather than euphoria[42]

Reasons include:[7]

- To self-mediate insomnia
- Self-medicate anxiety
- Get drunk without the hangover
- Reduce crash from stimulants
- To zone out
- To take the edge off
- To isolate themselves from prison surroundings
- To substitute for other substances
- To calm anxiety post stimulant use.

Use in opioid treatment programs

There is evidence that quetiapine pharmacokinetically can increase serum levels of methadone,[68] although predominantly it was mixed with other sedative medications rather than methadone.[66]
Case report of a person using quetiapine to potentiate a high from their suboxone[69]

How is it used in substance use – what is happening in the brain?

- **Poorly understood!** [7]
- Interplay between serotonergic, noradrenaline, dopamine and cholinergic systems[8, 30]

One mechanism is potent antagonism of H_1 (which is not mediated by D_1 and D_2 blocking due to quetiapine's lower affinity for these receptors[9]) – resulting in increasing dopaminergic activity in the nucleus accumbens – which is higher in quetiapine than other SGAs[7, 8, 30]

There are also animal studies that show that co-administration of quetiapine with amphetamine resulted in an anxiolytic effects (from the quetiapine) that did not have an effect on the reward properties of the amphetamine.[70]

There are animal studies that would indicate that the reinforcement from quetiapine use was enough to result in repeated self-administration[71]

Harms from quetiapine use

Adverse events associated with quetiapine misuse:[62]

- Sedation (51-54%)
- Tachycardia (23-25%)
- Slurred speech (7-8%)
- Dizziness (5-6%)
- Hypotension (5-6%)
- Agitation/irritability (5%)
- Confusion (4%)
- Ataxia (3-4%)
- Nausea (2%)
- Seizures (1%)
- Respiratory depression (1%)
- Coma (1%)

Long-term harms from quetiapine use

Quetiapine even if therapeutically indicated is associated with significant risks.

- Cardiovascular risk – there is an increased risk of QTc prolongation – risk of arrythmias particularly in combination with other medication that prolongs it[72]
- Orthostatic (or postural) hypotension[71] – can increase risk of falls[73]

- Metabolic factors – weight gain, elevated plasma triglycerides and cholesterol and more rarely hyperglycaemia can occur with quetiapine even at low doses [74, 75]
- Extrapyramidal effects – although lower than other antipsychotics (~10%) they do still occur[2, 3]

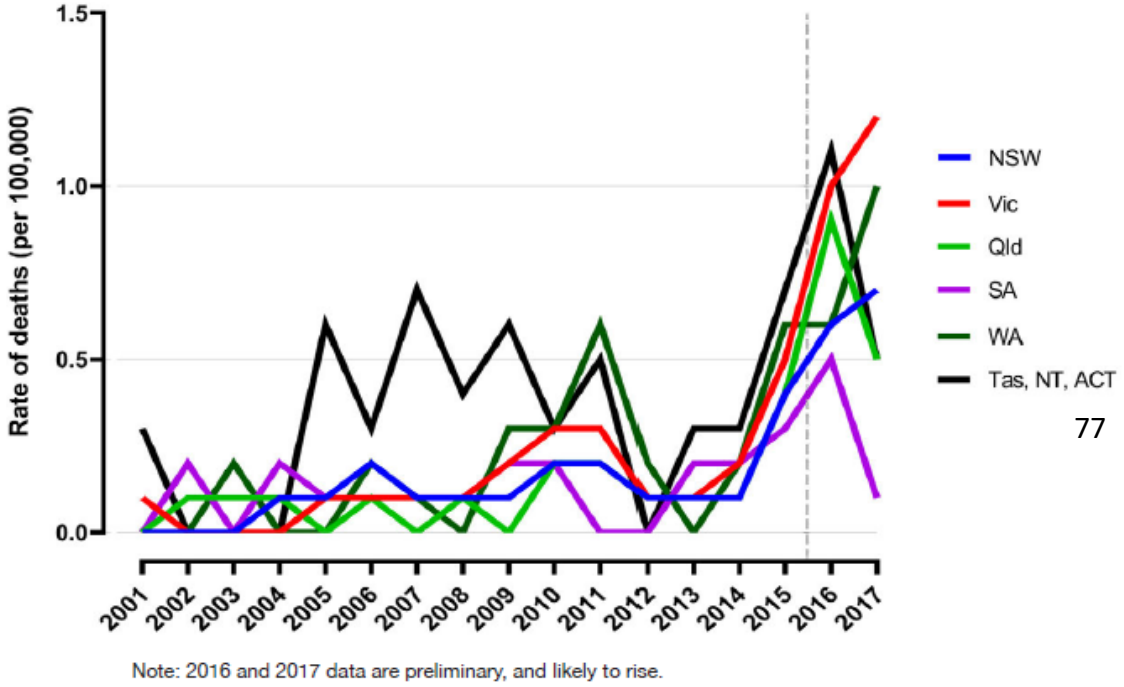
Harms from Quetiapine – overdoses

Overdoses of SGAs are considered relatively mild[76]

- Documented increase in mortality from quetiapine with a 7.4 fold increase in quetiapine-associated deaths in Victoria between 2006-2016.[25]
- Nationally there have been sharp increases in deaths with marked increases since 2013[77]

Quetiapine poisonings are increasing

- 6 fold increase in quetiapine related calls over a 10 year period in Victoria (2006-2016)[25]
- 5th most called about medications[25]
- Melbourne toxicology department showed that 9% of referrals were quetiapine related.[78]



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Harms from Quetiapine – overdoses

- Most common formulations of quetiapine in overdose were </= 100mg[25]
- 56% of presentations were off-label non-pbs approved prescribing indications.[25, 78]
- Just over half (58.6%) were co-ingested with other substances[25]

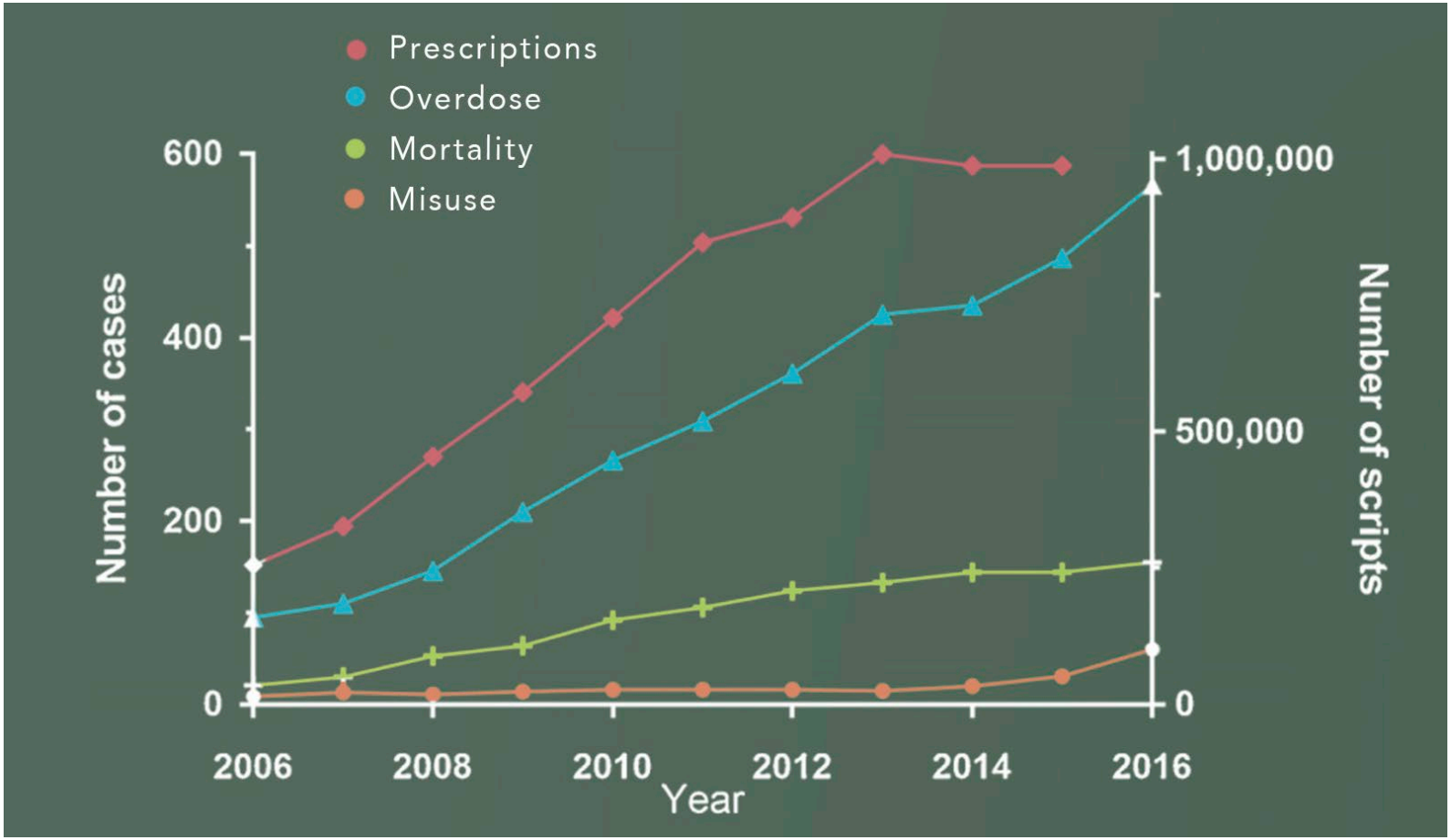


Fig. 2. Comparison of quetiapine overdose, misuse, mortality and prescription rates (VPIC, VIFM, PBS), 2006–2016 [25]

Harms from Quetiapine – overdoses

Symptoms of toxicity occurs one to two hours post ingestion[76] although this is significantly longer for extended release formulations[78]

Overdose symptoms[76, 78]

- Sedation, slurred speech,
- seizure
- Coma
- Anticholinergic symptoms (burry vision, dry mouth, constipation, urinary retention)
- Sinus tachycardia – prolonged QT interval (increased risk of arrythmias)
- Hypotension

**Co-ingestion with other substances (including alcohol) will also alter symptoms[76]

Harms from Quetiapine – overdoses

Treatment is largely supportive – i.e. treating the symptoms with stabilisation of the airway, breathing and circulation) [75]

- Benztropine for extrapyramidal effects
- Benzodiazepines for anticholinergic-induced agitation

Harms from Quetiapine – Dependence

Like all psychotropic medications abrupt interruption of supply or reduction will lead to "discontinuation" or withdrawal symptoms.[7]

There are a number of case reports that indicate quetiapine withdrawal syndrome, however there is limited information on the occurrence of this- with a handful of case-studies discussing it. [9, 79]

Quetiapine withdrawal

There is evidence of a withdrawal syndrome – but no current consensus of what is in it!

The description of the withdrawal syndrome here is based off drug information guidelines, and a systematic review that looked at literature reviews, case series and case reports

- According to product information – the incidence of symptoms in abrupt cessation was 16%[2, 3] - not based on supratherapeutic doses
- IR preparations have higher association with withdrawal symptoms than extended release[30]

Quetiapine withdrawal

Confounding of symptoms![79]

- Relapse – a return of episode that prompted drug treatment in the first place
- Recurrence – same as relapse but occurs later
- Rebound is return of original symptoms with greater intensity
- Withdrawal – psysiological and physiological responses to drug cessation
- Persistent post-withdrawal syndrome – more intense return to original disorder with potentially new symptoms.

Quetiapine withdrawal - symptoms

Common

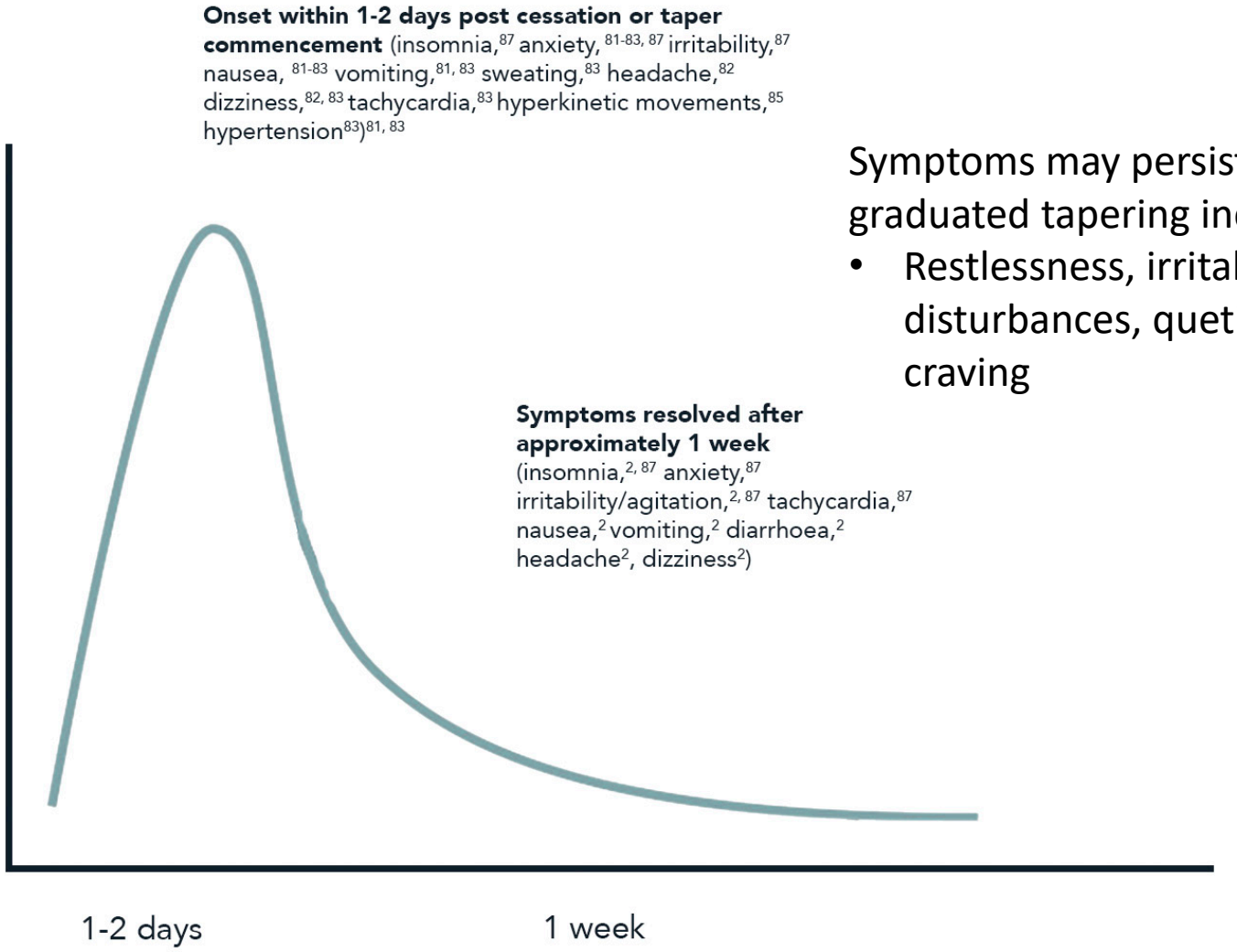
Physical symptoms	Psychiatric symptoms
Nausea, [2, 30, 81-84]	Insomnia / sleep distrubances[2, 30, 43, 84, 87, 88]
Diarrhoea[2, 30, 84]	Anxiety/ unsettled/ nervous/ restless[9, 43, 79, 81-83, 86-88]
Vomiting[2, 30, 83, 84]	Irritability/ agitated[2, 30, 43, 84, 87, 88]
Headache[2, 30, 43, 82, 84]	Dysphoria[30, 79, 88]
Dizziness[2, 30, 82-84]	Craving[30, 88]
Sweating[30, 83, 85, 86]	
Tachycardia[30, 83, 85, 87]	

Infrequent

- Fatigue[79]
- Back pain[79]
- Fever[79]
- Hyperkinetic movements (involuntary irregular jerking movement)[85, 89]
- Tremors[86]
- Hypertension[81, 83]
- palpitations[86]

Quetiapine withdrawal – Time period

Data was very inconsistent or not available – and primarily gained off case reports.



Symptoms may persist even on graduated tapering including[8, 82]

- Restlessness, irritability, sleep disturbances, quetiapine craving

Quetiapine withdrawal – Management

There is very little guidance for management of withdrawal –
In the first instance – tapering is preferred over at least 1-2 weeks is advisable[90] – although depending on the dose a slower withdrawal would make symptoms more manageable.
Only recommendation was-prochlorperazine for nausea [82]

Note: this is only for off-label use! When discontinuing chronic antipsychotic therapy in patients with schizophrenia or bipolar disorder, decreasing the dose very gradually over months to years with close monitoring is suggested to allow for detection of prodromal symptoms of disease recurrence[90]

Recommend that you contact your local clinical advisory service! Queensland ADCAS **1800 290 928**

Quetiapine.. Is it helpful or hazardous?

More research is needed!! – particularly to clarify what populations of people will benefit best from using quetiapine – particularly in substance use populations

- There is some preliminary evidence that quetiapine anxiolytic and sedative effects and increased dopamine activity in the PFC have been helpful – particularly in those with comorbid substance and mental health conditions
- There is also evidence of risk of misuse, significant side effects and overdose risk

Like all medication – it is neither good nor bad – it is arguably not the "safe" alternative to benzodiazepines

Judicious prescribing that keeps in mind and mitigates the potential risks will help alleviate many of the harms from this medication – and getting specialist involvement in early!

Articles for further information

Brett J. Concerns about quetiapine. Australian prescriber. 2015;38(3):95-7.doi: 10.18773/austprescr.2015.032

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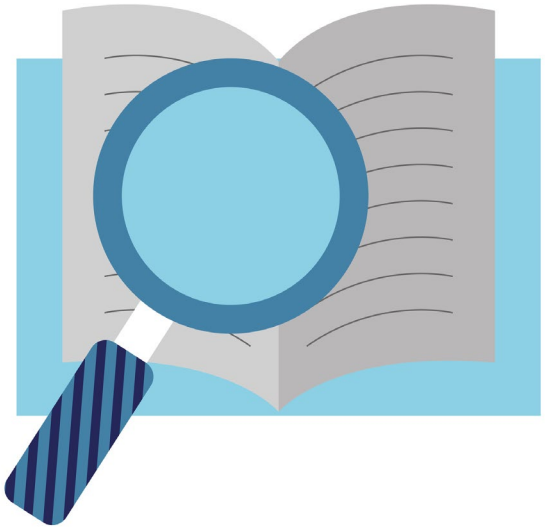

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