Clinical Course and Recommendations for the Management of Benzodiazepine Withdrawal Delirium: A Systematic Review of Case Reports

MAYO CLINIC

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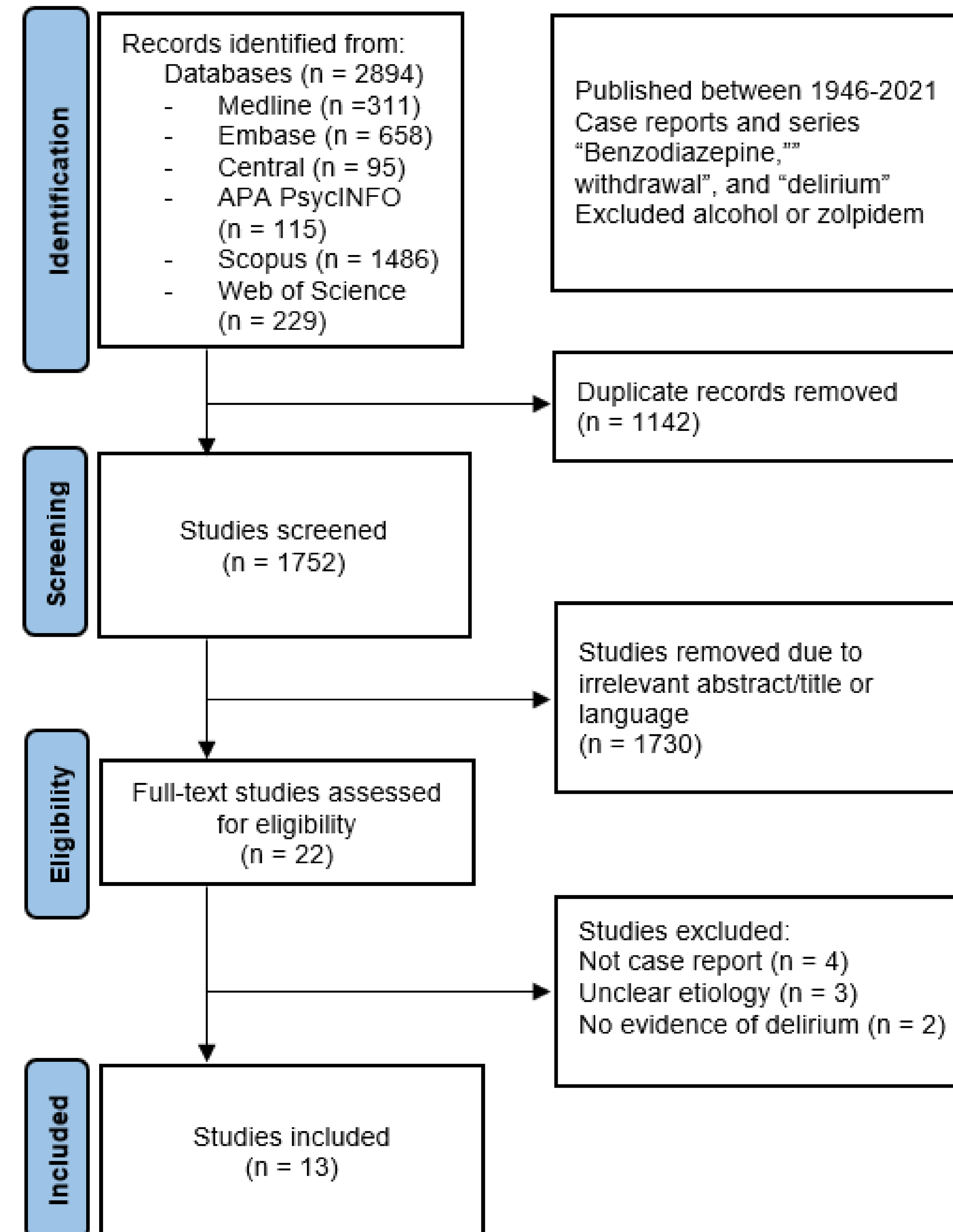
BACKGROUND

- Benzodiazepines are widely prescribed medications (Olfson 2015)
- Withdrawal can cause a variety of symptoms including tremors, anxiety, seizures, and delirium
- The literature surrounding GABAergic **withdrawal delirium** (**WD**) has focused more prominently on alcohol WD
- We present a systematic review of benzodiazepine WD case reports with the goal to consolidate the literature on its common presentation and treatment

RESULTS

- Total: 13 studies, 17 cases
- Age: 56.1 ± 18.1 (mean ± SD)
- Lorazepam mg equivalent (LME): 0.5 to 20
- Pre-WD duration on benzodiazepine: 6 weeks to years
- Onset: in 1 day to 13 days
- Duration: 1 day to 4 weeks
- Context: Iatrogenic discontinuation, self-discontinuation, switching, or tapering down
- Treatment: re-initiation of benzodiazepine ± antipsychotics for additional management

PRISMA FLOW DIAGRAM



CHARACTERISTICS OF THE INCLUDED CASES

Year	First author	Age /Sex	Pre-delirium benzodiazepine/ dose/duration	LME	Psych Dx	Medical history	Onset/ Duration of delirium	Delirium symptoms	Context	Treatment
2021	Lutz	50s/M	clonazepam 0.5 mg	1	MDD, PTSD	NR	4 days/ NR	paranoia, flight of idea	DC following spinal surgery	clonazepam
2019	Reeves	69/F	lorazepam 6 mg >10 yr	6	GAD	CAD, HTN, hypothyroid-ism	NR/ 4 weeks	disorientation, cognitive dysfunction	irregular self-administration	diazepam
2011	Bosshart	64/F	lorazepam 5-10mg x1 yr	5-10	MDD, AUD, Benzo UD, NCD	hypothyroidi sm HTN	NR/ in hours	psychomotor agitation loosening association incomprehensible speech, memory deficits	switch from lorazepam to diazepam	lorazepam, haloperidol
1998	Moss	70/M 72/F 84/M	lorazepam 3 mg x3 mo clonazepam 0.5 mg x 2 yr alprazolam 0.25 mg	3 1 0.5	NR	CAD s/p bypass	3 days/ 2 days 6 days/ 2 wks	restless, V/H, disorientation, delusion slurred speech	iatrogenic DC following admission for surgery	lorazepam clonazepam alprazolam
1998	Zalsman	65/M	alprazolam 6 mg x 6 wk	12	MDD Panic	NR	1 day/ 1 day	disorientation, paranoia, agitation, V/H	rapid tapering down	alprazolam
1991	Freiberger	48/M	alprazolam 5 mg x yr	10	NR	CAD	1 day/ 1 wk	restlessness, remove lines, hallucinations, disorientation	DC following surgery	lorazepam, midazolam, haloperidol
1991	Moss	68/F	lorazepam 2 mg x 3 mo	2	NR	abdominal aneurysm	6 days/ 1 day	disorientation, paranoid, V/H	iatrogenic DC following admission for surgery	haloperidol lorazepam
1989	Hauser	29/M 30/F 29/M	clorazepate 45mg clonazepam 4 mg clorazepate 30 mg	6 8 4	NR MDD NR	seizure disorder	3 days/ NR 2 days/ NR 13 days/ 5 days	restlessness, disorientation, hallucination	tapered in the research setting	clorazepate haloperidol +lorazepam diazepam
1987	Heritch	53/M	triazolam 5 mg x 3 mo	20	AUD	keratitis	2 days/ NR	irritability, confusion, hallucinations, paranoia	DC following admission	lorazepam
1985	Zipursky	68/M	alprazolam 1.5 mg x 11 mo	3	MDD	NR	2 days/ 1 wk	confusion, paranoid delusion, V/H, A/H	tapering	alprazolam
1984	Levy	77/M	alprazolam 5 mg x 3 mo	10	GAD Insomnia	degenerativ e joint disease	1 day/ 1 wk	agitation, disorientation, V/H seizures dysarthria	DC given lack of refill	NR
1978	Allgulander	30/F	clorazepate 60 mg x 3 mo	8	Benzo UD	NR	8 days/ NR	confusion V/H, A/H	self-DC	clomethiazole
1977	Dysken	48/M	diazepam 15-30mg x 7 yr	2.5-5	MDD, AUD	NR	8 days/ 1 day	confusion, disorientation, incoherent speech, loosening of association	DC following admission	chlorpromazine, diazepam

DISCUSSION

- A lack of research on benzodiazepine WD vs uncomplicated benzodiazepine withdrawal
- Risk factors for benzodiazepine withdrawal
  - high dose, long-term use, and short half-life benzodiazepine
- Unclear whether these risk factors correlate to WD
- Re-initiation of benzodiazepine remains as the standard of care for withdrawal and WD
- In cases of severely agitated, collateral strategies, such as in delirium tremens (Schuckit 2014), deserve further investigation
- Routine use of prescription drug monitoring programs can be of great benefit as preventative measures

CONCLUSIONS

- Benzodiazepine WD can manifest with various psychopathology
- Prompt re-initiation of benzodiazepine remains the mainstay of treatment
- Future study of large populations is needed to quantify risk profiles of benzodiazepine WD and investigate collateral strategies

REFERENCES

1. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry 2015 Feb;72(2):136-142
2. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med 2014;371(22): 2109-2113

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