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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

OFF-LABEL STIMULANT PRESCRIBING

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project ECHO

SPEAKER DISCLOSURES

I have no conflicts of interest to disclose.

Planner disclosures

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Discuss off-label stimulant prescribing
2. Highlight off-label prescribing as a general issue
3. Suggest how to potentially improve practice

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These are my views and not the official views of the VA, or the University of Washington.

This talk concerns off label uses of stimulants. It is not an endorsement of these uses but aims to provide information about improving prescribing around these uses.

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Defining off-label prescribing

Off-label: prescribed for an indication that is not FDA approved

--large parts of practice, especially in MH, are off-label (estimates vary, depends on setting)

--off-label is not inherently “worse” prescribing than on-label (or “indicated”), and at times it’s the only option because many aspects of our practice do not, and will never have, direct evidence/studies (for various reasons)

--there isn’t clear consensus on how to discuss or document off-label uses

--there generally aren’t strong recommendations from guidelines, either

How do stimulants fit into the off-label picture?

--they are highly controlled substances

--they have very narrow indications

--they can be highly useful medications likely with a low NNT

--they have been used in many off-label situations

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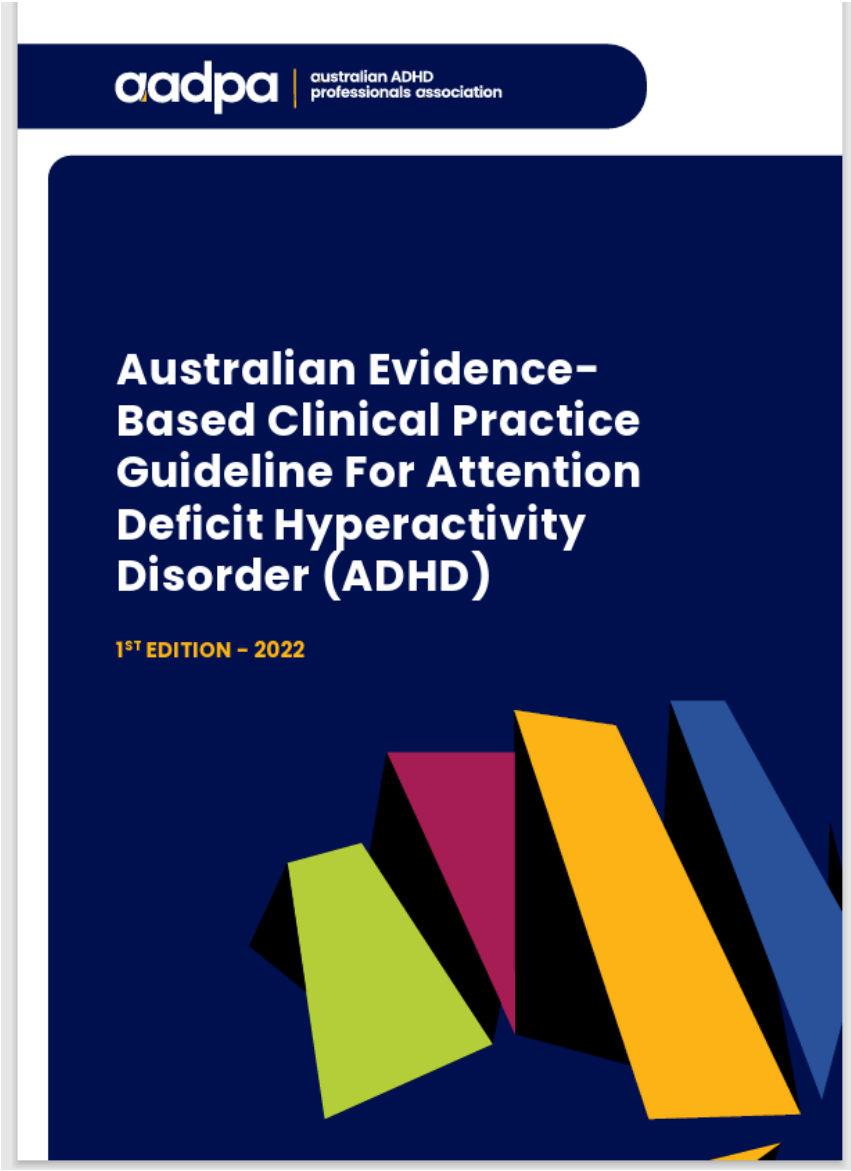

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(Professionals should) “have an adequate knowledge of applicable laws and regulations in the jurisdiction in which they are practicing, particularly as they relate to medications, prescribing, off-label prescribing, safety and use of stimulants” --p. 61

What are the FDA-approved, **on-label** uses of stimulants in adults?

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What are the FDA-approved, **on-label** uses of stimulants in adults?

--ADHD (of course!) – amphetamine and methylphenidate

--binge eating disorder -- lisdexamfetamine (Vyvanse)

--narcolepsy -- amphetamine and methylphenidate

Discussion:

What are off-label uses of stimulant in YOUR practice?

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What are off-label uses of stimulants? An overview.

Relatively **more wide use/supported:**
--depression (geriatric depression, treatment-resistant depression)
--post-traumatic brain injury (TBI)

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Depression: limited literature

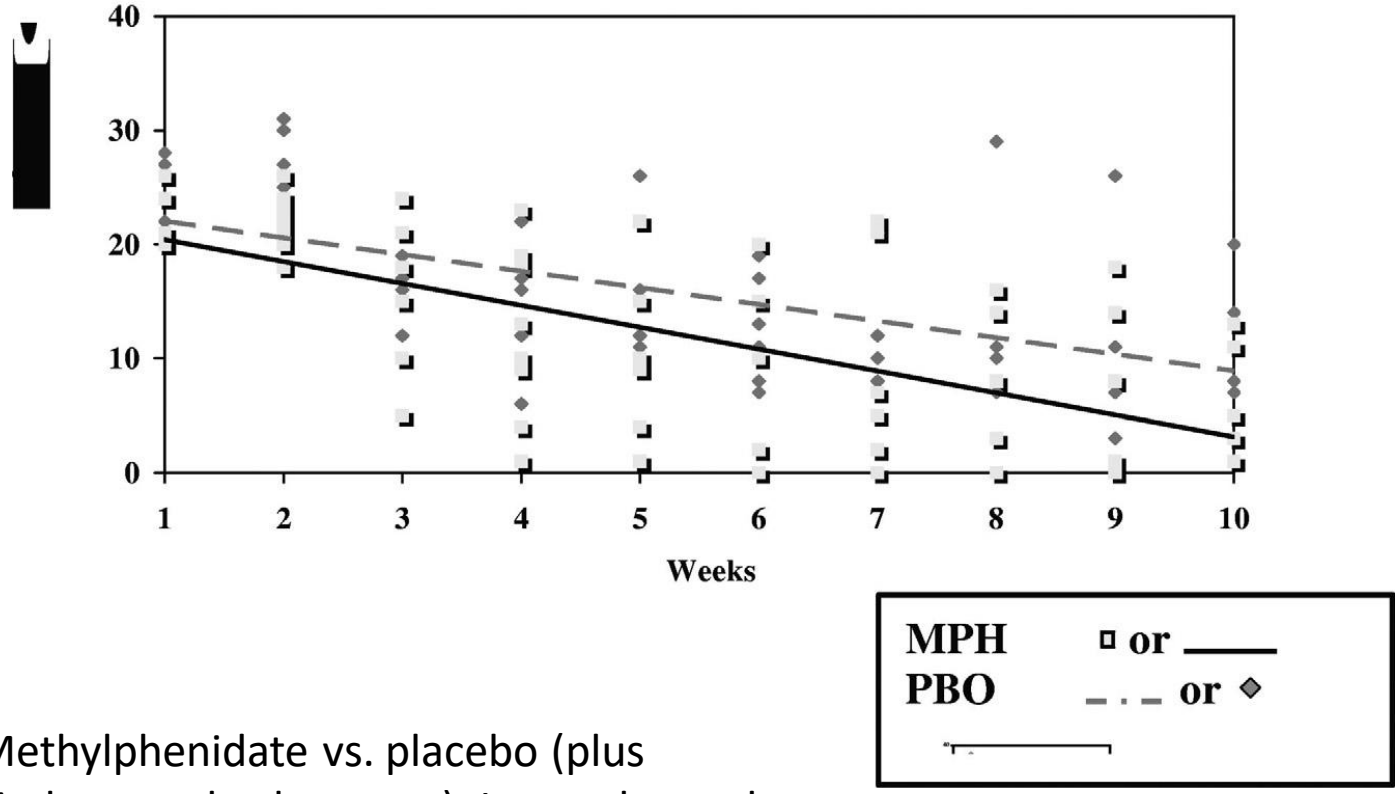
"MPH appears to be the most effective when combined with citalopram and used short-term." (review; Smith et al., Int. J. Ger. Psych. 2021)

Citalopram + MPH – antidepressant acceleration, very small study (Lavretsky, Amer. J. Geri. Psych. 2006)

Modafinil/armodafinil have some support and may be safer (review; Corp et al., J. Clin. Psych., 2014)

Informal conclusions: there is very modest evidence for using stimulants in depression. Some have suggested they may be more effective in older populations, but this is not strongly supported. In this setting, specific individual agents have even less support.

How does this affect clinical practice? This is a very typical setting for off-label uses of any kind (at least in MH)



Methylphenidate vs. placebo (plus citalopram, both groups). Lavretsky et al., Am. J. Geri. Psych., 2006.

Post-Traumatic Brain Injury (TBI): also very modest literature

--I could find no formal consensus or definitive recommendations; however:

--it has been suggested that stimulants can improve cognition (and possibly motor function) post-mild to moderate TBI

--INCOG 2.0 recommendations: expert consensus group on cognitive rehabilitation post-TBI—recommends methylphenidate (J. Head Trauma Rehab., 2020)

--there is little systematic evidence for use of specific agents; these have included methylphenidate (though another recent review suggested amantadine had the best evidence, though not technically a stimulant; Kakehi and Tompkins, Ann. Pharmacother., 2021)

Other, less-supported but potential uses of stimulants, off-label

--fatigue in neurological conditions (non-MH)

--excess daytime sleepiness (off-label, vs. modafinil/armodafinil which are on-label)

--PTSD

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Multiple sclerosis related fatigue (non-MH/neurology):

-recent study (Nourbakhsh et al., Lancet Neurol. 2021): comparing amantadine, methylphenidate, modafinil and placebo

--no difference between treatment arms in terms of effects on fatigue

--active treatment groups had more adverse effects

--it was suggested *beneficial* effects are due to placebo

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	Mean score	Estimated mean score				
	Baseline (n=136)	Placebo (n=123)	Amantadine (n=124)	Modafinil (n=124)	Methylphenidate (n=127)	p value for the overall medication effect*
Modified Fatigue Impact Scale Total†	51·3 (49·0–53·6)	40·6 (38·2–43·1)	41·3 (38·8–43·7)	39·0 (36·6–41·4)	38·6 (36·2–41·0)	0·20
Neuro-QoL Fatigue T score‡	58·5 (57·6–59·4)	53·1 (51·9–54·3)	53·0 (51·7–54·2)	52·5 (51·3–53·8)	52·0 (50·8–53·2)	0·42
Epworth Sleepiness Scale‡	11·1 (10·2–11·9)	9·4 (8·7–10·1)	9·3 (8·6–10·1)	8·3 (7·6–9·1)	8·8 (8·1 to 9·6)	0·071
Modified Fatigue Impact Scale physical subscale§	24·1 (22·9–25·3)	18·9 (17·7–20·1)	19·5 (18·3–20·6)	18·4 (17·2–19·6)	18·0 (16·9–19·2)	0·21
Modified Fatigue Impact Scale cognitive subscale§	22·4 (21·0–23·7)	17·8 (16·6–19·0)	18·0 (16·8–19·2)	17·0 (15·8–18·2)	17·2 (16·0–18·4)	0·42
Modified Fatigue Impact Scale psychosocial subscale§	4·8 (4·5–5·2)	3·9 (3·6–4·2)	3·9 (3·6–4·2)	3·6 (3·3–3·9)	3·4 (3·1–3·7)	0·028

Data are mean (95% CI). Neuro-QoL=Quality of Life in Neurological Disorders. *p value for the overall medication effect in the mixed-effect regression model. †Prespecified primary outcome. ‡Prespecified secondary outcomes. §Post-hoc exploratory outcomes. The fixed predictors were study medications, treatment sequence, treatment period, the baseline level of the outcome, and the study site. Patients were the random effect.

Table 2: **Mean baseline values and estimated means for each medication**

Nourbakhsh et al. (Lancet Neurology, 2021)

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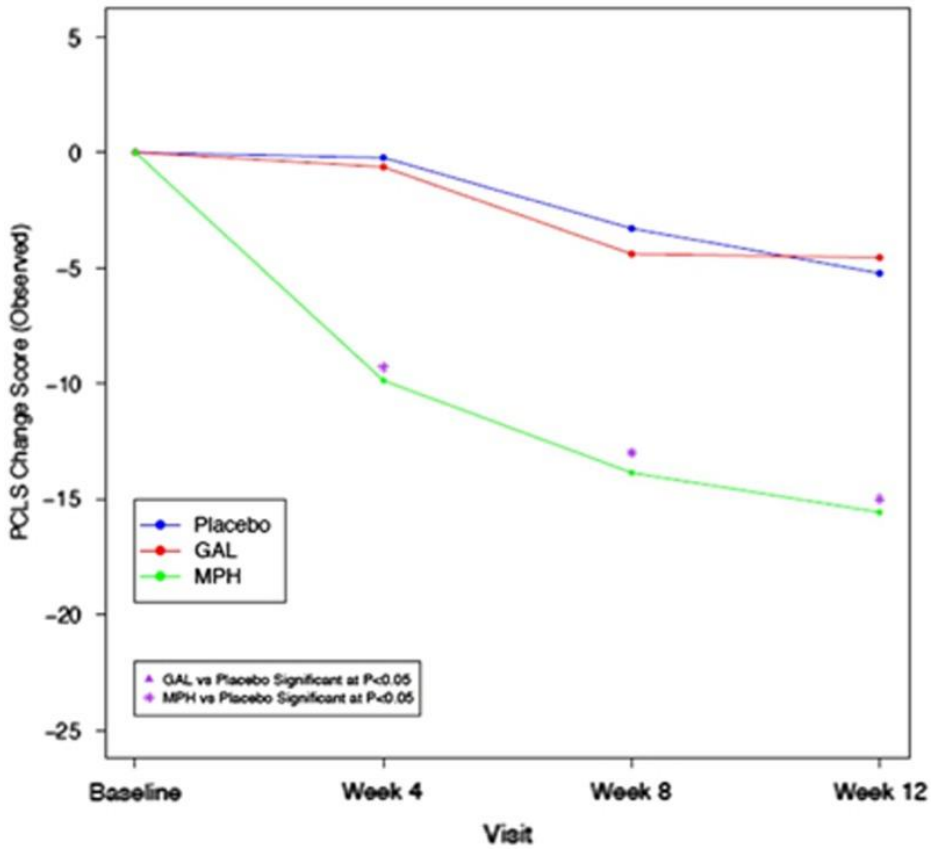
PTSD:

--medications for PTSD are few, and not thought to be highly effective (and overall, less effective than therapy); there is an urgent need for medications that might help with any and all aspects of PTSD

-emerging area under study including at VA

-preliminary trial showed promise for attentional improvement with MPH, notable without exacerbation of anxiety or hypervigilance



Methylphenidate vs. galantamine vs. placebo; results on PCL-5. From Mcallister et al. (Neuropsychopharmacology, 2016)

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What are some off-label uses of stimulants that you might not recommend or are less supported?

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What are some off-label uses of stimulants that you might not recommend?

--weight loss (amphetamines; non-amphetamine phentermine more accepted but probably not the best practice?)

--performance enhancement (“nootropics”)

--apathy in dementia (very limited results, clinical concerns)

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National QI project:

Psychotropic Drug Safety Initiative (PDSI)

--one element: using dashboard data to provide information for improving prescribing

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Rationale

To identify patients who may need re-evaluation of the rationale for their stimulant prescription

Guidance

Evaluate clinical appropriateness of the stimulant prescriptive therapy. If appropriate, ensure clinical documentation is in patient's electronic health record.

PDSI Phase 5, Step 2 metric: off-label stimulant use

VHA patients with an outpatient stimulant prescription who do not have an active FDA indicated diagnosis for a stimulant (i.e., ADHD, BED, narcolepsy)

VHA patients with an outpatient stimulant prescription

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AMPHETAMINE
AMPHETAMINE RESIN COMPLEX
AMPHETAMINE/DEXTROAMPHETAMINE
DEXMETHYLPHENIDATE
DEXMETHYLPHENIDATE/SERDEXMETHYLPHENIDATE
DEXTROAMPHETAMINE
LISDEXAMFETAMINE
METHAMPHETAMINE
METHYLPHENIDATE

How much stimulant prescribing is off-label?

What are off-label uses of stimulant in the real world, courtesy of the PDSI QI project?

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How much of stimulant prescribing is off-label?

--depression, TBI and MS are very common conditions (and there are other off-label uses that are less frequent, as well)

--Limited prior data suggests off label stimulant prescribing is common, but possibly decreasingly so

--FY 2012 in VA: **59.9% of incident stimulant prescriptions were off label** (Westover et al., Addiction, 2017); concern for how this use might relate to subsequent misuse

--**40%** (Safer et al., J. Attn. Disorders, 2015)

--**community sample 17.6% of stimulant prescribing was off label**, appeared that this was almost entirely for depression (Vijay et al., PLOS ONE, 2018)

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PDSI Phase 5, Step 2:

off-label measure:

National data: 16.9% (Numerator: 9776 / Denominator: 57684)

Puget Sound example: 22.3% (272 patients meeting measure criteria for off-label use)

--for perspective: this is not a large number in absolute terms, but surprisingly large proportional to total stimulant use at our facility

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Patient Count: 268		What factors contribute to my patient's risk?		How can I follow-up with this patient?		
Patient Information	Measures Not Met	Relevant Diagnoses	Relevant Medications	Care Providers	Recent Appts	Upcoming Appts
	Off_Label_RxStim ☑ Monitoring_RxStim ☑ Vitals in past 6 mo: Yes; No UDS in past year	**Mental Health** Any MH diagnosis Depression - MDD and other depression **Medical Indications** Medical Indications for Benzodiazepine **Medical Indication** Medical indications for antidepressant **Medical** Traumatic Brain Injury **Drug Indication** MH or medical indication for Antidepressant MH or medical indication for benzodiazepines **Chronic Respiratory Diseases** Chronic Respiratory Diseases	**VA outpatient med** BUPROPION Months in Treatment: 36 • Schreiber,Matthew A DICYCLOMINE Months in Treatment: 37 • Ham,Erin K FLUOXETINE Months in Treatment: 38 • Schreiber,Matthew A GABAPENTIN Months in Treatment: 18 • Ham,Erin K AMPHETAMINE/DEXTROAMPHETAMINE Months in Treatment: 12 • Schreiber,Matthew A	**BHIP TEAM:** • Pug Bhip Mhc Alpha **MH Tx Coordinator:** • Schreiber,Matthew A **Outpatient Stop Codes:** • Gen Mh Outpatient • Primary Care **PACT Team:** • Sea Rainier 16 **PDSI Prescriber:** • Schreiber,Matthew A **Primary Care Provider:** • Hernandez,Laura E	**OtherRecent** • 9/14/2023 Polytrauma/Tbi Ind **Primary Care Appointment** • 5/24/2023 Primary Care/Medicine **Specialty Pain** • 4/27/2023 Pain Clinic **MH Appointment** • 7/18/2023 Mental Health Clinic - Ind	**OtherRecent** • 10/16/2023 Polytrauma/Tbi Ind **Primary Care Appointment** None **Specialty Pain** None **MH Appointment** None

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Patient Count: 268		What factors contribute to my patient's risk?		How can I follow-up with this patient?		
Patient Information	Measures Not Met	Relevant Diagnoses	Relevant Medications	Care Providers	Recent Appts	Upcoming Appts
Active Station(s) • (663) Puget Sound HCS Click to confirm patient review No Review Performed	Off_Label_RxStim ☑ Monitoring_RxStim ☑ Vitals in past 6 mo: Yes; No UDS in past year	**Mental Health** Any MH diagnosis Depression - MDD and other depression **Medical Indications** Medical Indications for Benzodiazepine **Medical Indication** Medical indications for antidepressant **Medical** Traumatic Brain Injury **Drug Indication** MH or medical indication for Antidepressant MH or medical indication for benzodiazepines **Chronic Respiratory Diseases** Chronic Respiratory Diseases	**VA outpatient med** BUPROPION Months in Treatment: 36 • Schreiber,Matthew A DICYCLOMINE Months in Treatment: 37 • Ham,Erin K FLUOXETINE Months in Treatment: 38 • Schreiber,Matthew A GABAPENTIN Months in Treatment: 18 • Ham,Erin K AMPHETAMINE/DEXTROAMPHETAMINE Months in Treatment: 12 • Schreiber,Matthew A	**BHIP TEAM:** • Pug Bhip Mhc Alpha **MH Tx Coordinator:** • Schreiber,Matthew A **Outpatient Stop Codes:** • Gen Mh Outpatient • Primary Care **PACT Team:** • Sea Rainier 16 **PDSI Prescriber:** • Schreiber,Matthew A **Primary Care Provider:** • Hernandez,Laura E	**OtherRecent** • 9/14/2023 Polytrauma/Tbi Ind **Primary Care Appointment** • 5/24/2023 Primary Care/Medicine **Specialty Pain** • 4/27/2023 Pain Clinic **MH Appointment** • 7/18/2023 Mental Health Clinic - Ind	**OtherRecent** • 10/16/2023 Polytrauma/Tbi Ind **Primary Care Appointment** None **Specialty Pain** None **MH Appointment** None

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PDSI - Patient Review - DOES NOT WRITE TO CPRS

Using the toolbar above, please enter patient review information, and then click 'View Report'.

IMPORTANT

Information entered into this report facilitates patient review process and does NOT constitute medical record documentation. Pleae use CPRS to document relevant clinical information.

Patient Summary

Patient Information	Measures Not Met	Recent Appts	Upcoming Appts	Providers
	Off_Label_RxStim ☑ Monitoring_RxStim ☑	No VA Contact in the Last Year		

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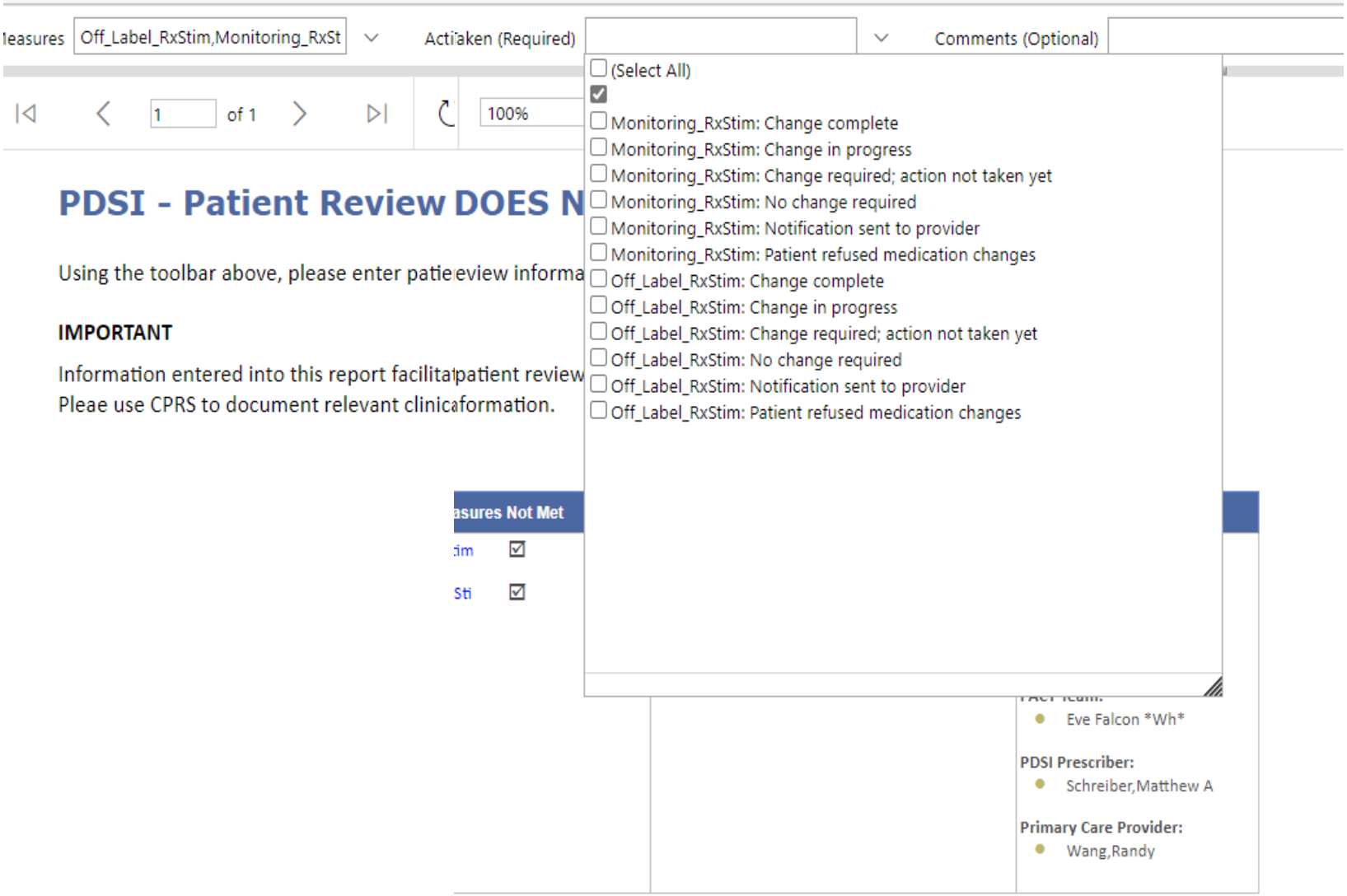

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Off_Label_RxStim: Change complete
Off_Label_RxStim: Change in progress
Off_Label_RxStim: Change required; action not taken yet
Off_Label_RxStim: No change required
Off_Label_RxStim: Notification sent to provider
Off_Label_RxStim: Patient refused medication changes

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Thoughts on using this measure: application to improving clinical practice.

52 stimulant-prescribed patients

6 meet the off-label measure—reviewed for the measure

Options (some): continue stimulant, make changes to prescribing, make changes/update documentation

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Patient 1: history of TBI-associated cognitive issues

Patient 2: older patient with depression, medical comorbidities (but not precluding stimulant use) and prominent low energy

Patient 3: ADHD missing from problem list, added

Patient 4: older patient with depression, prominent low energy and daytime fatigue, other medications may be playing a role

Patient 5: prescribed for MS-related fatigue by Neurology

Patient 6: ADHD on problem list, but no recent VA contact, updated problem list, requested follow up

Also noted in larger sample: community prescribed stimulant, clearly for ADHD, no ADHD diagnosis in chart (no VA MH prescriber)

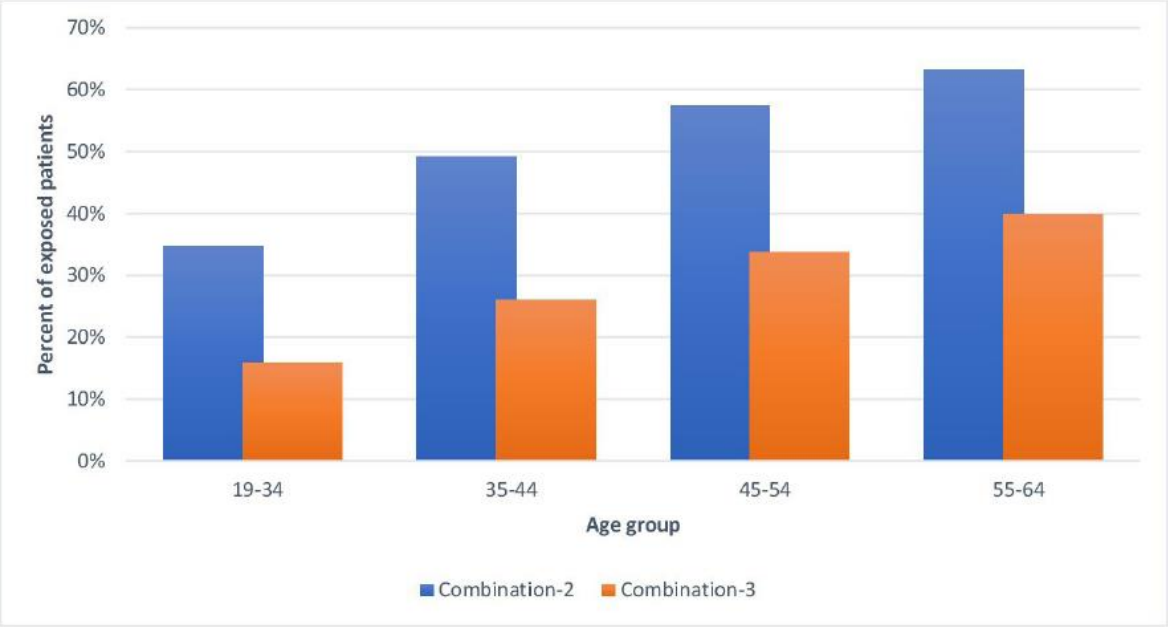

Figure 2 Prevalence of combination therapy among stimulant users by age group, 2020 combination therapy with stimulants and one or more other psychiatric drugs (n=121 781, Combination-2) or two or more other psychiatric drugs (n=66 996, Combination-3); MarketScan Research Databases, 2019–2020, outpatient pharmaceutical claims.

Moore et al. (BMJ Open, 2023)

Off-label prescribing advice:

The law and practice of off-label prescribing and physician promotion. Syed et al., J. Am. Acad. Psych. Law (2021)

Ten common questions (and their answers) about off-label drug use. Wittich et al., Mayo Clinic Proc. (2012)

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Reflections for future practice:

--off label stimulant prescribing is not unusual, in fact it is relatively common

--it is **NOT** inherently “wrong” but should be done with care and your usual thoughtfulness

--as with all off-label prescribing, consider documenting your rationale, and your awareness that the use is off-label

--consider discussing off label use directly with patients in your practice as part of shared decision-making (though this is not considered mandatory) , and documenting your discussion