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Underutilization of Pharmacotherapy for Treatment of Alcohol Use Disorders Part II-Results from a Survey of Practices among North Carolina Mental Health Providers and Brief Review of Efficacy of Available Pharmacotherapies

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Abstract

Introduction: Alcohol is the third leading cause of preventable death worldwide. There is substantial risk for development of alcohol use disorder among those with psychiatric disorders, complicating their care. Despite extensive evidence in support from controlled trials and from expert opinion, medication-assisted treatment has had low levels of penetration in practice. Only 3% of sufferers receive FDA-approved treatment.

The goal of this survey is to explore potential causes of underutilization of evidence-based pharmacotherapeutical agents in the treatment of alcohol use. Secondary, we analyze differences in practice patterns between different academic institutions, facilities specializing in chemical dependence treatment, and general community practitioners. We are aware of no prior study that has attempted to evaluate these factors.

Methods: An online questionnaire was designed in Qualtrics and distributed through the use of an anonymous link. Target participants were members of the Psychiatry departments of four academic institutions in NC, community mental health providers, prescribers from chemical dependence treatment facilities, and Veteran Affairs psychiatrists. A total of 170 participated, an 85% response rate. Data was analyzed using Qualtrics software as well as by a statistician.

Results: A significant portion of psychiatric patients have comorbid alcohol use, and despite patient interest, medications are rarely utilized in both academic as well as chemical dependence facilities-20% of respondents never prescribed any. Reasons mainly include lack of provider knowledge of available medications (r=-0.277, n=136, p=0.001), prescribing guidelines (r=-0.265, n=136, p=0.002) and dosing (r=-0.245, n=136, p=0.004). Provider's attitude towards substance use treatment also affects prescribing (r=-0.21, n=136, p=0.014). Those who do prescribe seem to favor off-label medications and avoid Naltrexone IM formulation. Providers acknowledge that the majority of those with alcohol use disorders have medical conditions caused or affected by the ongoing use. Instituting medications leads to positive experiences: patients maintain sobriety longer, have less legal problems and are better able to engage in their care.

Conclusion: In the treatment of alcohol use, guidelines recommend FDA approved medications in conjunction with bio psychosocial interventions. Global assessment indicates prescribers mainly avoid pharmacotherapy due to lack of comfort and knowledge. There may also be financial barriers in a current alcohol treatment system that is traditionally non-medically oriented. Although it is recommended to start with FDA approved medications, off-label use is high. Despite positive implications noted when medications are instituted, providers' ambivalence continues. As part of our daily practices, general psychiatrists should gain confidence in using evidence-based, FDA approved, medications in treatment of alcohol use disorders.

Keywords: Alcohol; Pharmacotherapy; Opioid

Introduction

Alcohol use disorder (AUD) is a global problem affecting 20 million Americans. It is associated with significant human and financial costs [1,2] and is the third leading cause of preventable death worldwide [3]. With 80% of the adolescent population having used alcohol this year and with the emergence of new more dangerous formulations such as Palcohol, prevalence of alcohol-related problems can be expected to rise [4]. A greater prevalence is noted in clinical populations, especially those that are undergoing psychiatric treatment. In fact those with mental illness consume 38% of all alcohol [5]. Ongoing use complicates the course of medical and psychiatric conditions and carries significant social exclusion.

Despite an increase in psychotropic use for treatment of mental health illnesses in the past decade, pharmacotherapy for alcohol use is underutilized. Only 3% of sufferers receive FDA-approved treatment [1]. Management today remains largely limited to episodic short inpatient detoxifications and psychosocial therapies. Evidence indicates that recovery rates are highest when addiction treatment that monitors abstinence is continuous. Nevertheless most often alcohol addiction is treated in discrete episodes upon relapse. Neuroscience continues to support the brain disease model of addiction in which chronic drug use triggers neuroplastic changes, fostering ongoing use. Pharmacotherapy allows better control over cravings, enabling sobriety while psychosocial interventions improve impulse control [6]. There are diverse pharmacological treatment options that can be pursued with minimal disruption to home and work life. Despite modest effect sizes, efficacy has been demonstrated as these provide an important improvement in relapse rate. Although recommended by experts for "moderate" and "severe" alcohol use disorders, medication assisted treatment is underutilized in most settings where alcohol use disorders are addressed [7,8]. These individuals suffer from a potentially fatal chronic disease characterized by high post treatment recidivism.

Objective

The goal of this survey was to explore potential causes of underutilization for evidence-based pharmacotherapeutical agents in the treatment of AUD sufferers. The main hypothesis tested was that underutilization of such pharmaceuticals is associated with attitude about training with some secondary impact from insurers. The extent to which the various agents are used is characterized as well as how practices vary among academic practitioners, community, veteran affairs, and those treating primarily chemical dependence treatment facilities. To our knowledge, no prior study has attempted to evaluate the reason for provider resistance to use of medication-assisted treatment in AUD. Available medications and evidence of their efficacy are also reviewed with guidance for prescribers.

Pharmacotherapies for AUD

There are three medications approved by FDA for management of alcohol dependence or relapse to alcohol use: Disulfiram, Acamprosate and Naltrexone [8]. These have proven efficacy when part of a comprehensive plan that includes psychosocial therapies and social support [9]. There are also several off-label medications with evidence for efficacy. In addition to individual characteristics of each agent, when prescribing it is advised to consider patients' past experience with medication-assisted treatment, compliance, beliefs about efficacy of each agent and stigma, degree of motivation from abstinence versus reduction, medical comorbidities, and contraindications [10]. A goal of complete sobriety has best outcomes compared to controlled drinking [11]. Because alcohol use disorders are chronic illnesses, medications should be continued for at least 6 months to a year [10] with no current guidelines on the optimal duration of treatment, if any Table 1.

	Medication		Dosing Recommendation	Goal	Other Considerations
	Generic	Brand			
FDA-approved	Disulfiram	Antabuse	125-500 mg/day (250 mg/day is standard dose)	Complete abstinence	1. Disulfiram: ethanol reaction if consumed (nausea/vomiting/hypertension). This can even be triggered by small amounts of ethanol present in house hold products. Those with heart conditions may not tolerate such a reaction. 2. Careful with those on metronidazone. 3. Ensure adequate liver function.
	Acamprosate	Campral	666-999 mg TID	Relapse prevention (Reduce drinking, prevent cravings).	1. Ensure adequate renal function. 2. No hepatic metabolism. 3. No titration required but TID dosing may be challenging
	Naltrexone	Vivitrol, ReVia	50-100 mg/day PO 380 mg/month SC		1. Careful in those with chronic painon opioid therapy. 2. Ensure adequate liver function. 3. Injectable form addresses noncompliance and bypasses hepatic first pass metabolism
Off-label	Gabapentin	Neurontin	600-1800 mg/day divided doses	Relapse prevention (Reduce drinking, prevent cravings). Also improves sleep.	1. Ensure adequate renal function. 2. No hepatic metabolism.
	Topiramate	Topamax	25 mg/day, increase by 25-50 mg/day weekly to target dose 300 mg/day divided doses	Relapse prevention (Reduce drinking, prevent cravings)	1. Ensure adequate renal function. 2. Slow titration required. 3. Impaired memory concentration seems standard during concentration.
	Baclofen	Lioresal	5 mg TID for 3 days then increasing to 10 mg TID upto 20 mg TID	Limited studies show it promotes abstinence, reduces risk of relapse, alleviates cravings and anxiety	1. Ensure adequate renal function. 2. No hepatic metabolism.

	Ondansetron	Zofran	4 mcg/kg BID	Limited studies show it reduces number of drinks per day, increases days abstinent, reduces cravings	1. Ensure adequate liver function. 2. QTc prolongation risk-baseline EKG required. Contraindicated in congenitally long QTc syndromes and those at risk.

Table 1: Available FDA approved and off label pharmacotherapies for alcohol use disorder.

Disulfiram

Good candidates should be motivated to achieve complete abstinence, able to receive supervised dosing, medically stable and able to sustain a Disulfiram-reaction in the event of relapse [10]. Alcohol cannot be in the system at the time of Disulfiram initiation. There are several studies supporting the effectiveness of Disulfiram in relapse prevention [12,13]. At the same time, analysis of four placebo controlled randomized clinical trials produced mixed results with two trials showing a reduction in frequency of drinking days, but neither claimed improvement in relapse rates compared to placebo [14]. Compliance however seems to be the main focus of the therapy with level and quality of supervision of administration being the main driving force in efficacy [15,16].

Acamprosate

Typically initiated in patients who have had at least 1 week of sobriety, its effectiveness peaks at 1 week post-initiation [17,18]. Efficacy is mediated by its ability to blunt the negative symptoms during the period immediately post-withdrawal [19]. Aside from being abstinent, good candidates must have good renal function. An additional advantage is that it can be safely used in those with liver disease, on opioid pain regimen, or simply on multiple other medications. Although it is recommended to continue even if patients relapse, better outcomes have been achieved with patients motivated to achieve abstinence compared to those desiring to reduce frequency of drinking [20].

Naltrexone

Good candidates must be opioid free, for at least 1 week [21], and must desire to reduce frequency of drinking days. Systematic reviews of double blind, randomized, placebo controlled trials show oral Naltrexone has efficacy in decreasing relapse to heavy drinking [22-24], however most randomized controlled trials conducted included patients abstinent at treatment initiation. It is an especially useful medication for those with multiple relapses [25]. Poor compliance and treatment retention has led to the development of an extended release injectable Naltrexone formulation. Based on efficacy outcome studies, at least four days of sobriety are required prior to institution of this [26].

Gabapentin

Relying on its GABAergic activity, over the past decade several studies have examined the efficacy of Gabapentin in alcohol relapse prevention and decreasing drinking days. The evidence is mounting, and its safe adverse profile and cost effectiveness make it a suitable agent. Although there are several trials illustrating benefit, the amount of statistically significant evidence in trials with sound design and methodology is scant. Evidence for both monotherapy [27] and adjunctive therapy to Naltrexone [28] exists. The largest and most recent shows a trend towards dose related improvement in drinking outcomes however statistical significance at the higher doses is lacking [29]. Outcomes for improvement are positive in insomnia associated with alcohol dependence [30] as well as for cravings [31].

Topiramate

Believed to be due to glutamanergic antagonism, [32] Topiramate has been shown to reduce the number of drinks per day as well as heavy drinking days, and increase days of abstinence in several large randomized double blind placebo controlled trials [33-35]. Most recent trials have demonstrated efficacy in decreasing heavy drinking to safer levels and also found certain genotypes that might benefit from treatment with Topiramate [36]. The slow dose titration required to achieve the reported ranges of 100-300 mg prevents benefit from being observed until the fourth week [37]. In trials comparing Topiramate to Naltrexone, better outcomes in reducing intake and cravings have been reported with Topiramate [35,38,39].

Baclofen

Although there are limited studies to draw a significant clinical conclusion, the available data points to a positive direction [40-42]. The high doses reported in this literature have been investigated in a recent randomized controlled trial of 56 subjects [43]. Doses as high as 270 mg/day were well tolerated with good anti-craving effect and positive impact on days abstinent however not significant statistically. Several European studies are currently underway.

Ondansetron

The evidence is very limited. One randomized controlled trial showed significantly reduced drinking per day as well as greater days abstinent [44].

Nalmefeme

Evidence is very limited with current studies coming from Europe [45].

Combination treatment

Support for combination of these is limited with one study favoring addition of Gabapentin to Naltrexone to improve outcomes in the first six weeks of drinking cessation [46].

Promising evidence-Varenicline

On a behavioral level, nicotine and alcohol use are highly comorbid with one third of those with AUD having nicotine dependence and one fourth of those with nicotine dependence also have an AUD [47]. This partial alpha2 beta4 nicotinic acetylcholine receptor agonist approved for smoking cessation has been investigated in several trials of smokers with comorbid alcohol use with promising results. It is also

hypothesized that the nicotinic acetylcholine receptors may play a role in the rewarding effects of both substances [48-50]. Emerging evidence points there might be a signal in terms of reducing alcohol use in nonsmokers just as in smokers [51]. The effect size here in terms of reducing alcohol consumption at 6 weeks of Varenicline is double that reported with naltrexone and Acamprosate. It does not however seem to lead to complete abstinence. In smokers with comorbid alcohol use, based on this data, Varenicline works best if smoking is decreased as well.

Methods

A 19-question survey was designed and distributed via Qualtrics (https://www.qualtrics.com) to prescribers involved in treatment of those with mental health illnesses in North Carolina. Although the four major academic institutions (East Carolina University, University of North Carolina, Duke University and Wake Forest University) were targeted, the survey was also distributed through the state psychiatric association's newsletter to community and chemical dependence providers. The survey was initially distributed May 15, 2016 and was available for 1 month with 3 weekly reminders sent out to non-responders. Within our institution, response rate was 85%. The final number of participants who completed the survey was 170. Through the use of an individualized link, participants were anonymously electronically registered. Responses were completely anonymous with no IP addresses or personal identifiers being collected. Data was gathered and further analyzed by Qualtrics and also by a statistician. The study conductors have no disclosures and this study was exempt from East Carolina University Institutionalized Review Board (IRB) review (UMCIRB 16-000974).

Results

Among providers associated with academic institutions, close to half of patients seen in a primary psychiatric setting have comorbid alcohol use disorders yet only a fourth are on medications despite a majority of them demonstrating interested in treatment. For those, medications are prescribed for less than 30% of them with 20% of providers having never prescribed any. Even providers associated with chemical dependence facilities have reported that fewer than 25% of those interested in treatment receive medications. Reasons for this include lack of provider knowledge of available medications, prescribing guidelines, dosing, monitoring parameters and literature supporting their efficacy with some impact from insurance coverage of such medications. When employing a linear by linear χ^2 analysis, only knowledge of medication available (r=-0.277, n= 136, p=0.001), dosing (r=-0.245, n=136, p=0.004), and prescribing guidelines (r=-0.265, n=136, p=0.002) proved to be significantly associated with frequency of prescribing. Insurance coverage was not statistically significant, however believing that AUD should be treated separately from mental health was significantly associated with frequency of prescribing (r= -0.21, n=136, p=0.014).

As a general trend, those that prescribe favour off-label medications and particularly avoid Naltrexone IM, which is absent from most formulary at academic institutions. Providers associated with chemical dependence facilities favour off label medications and Disulfiram greatly over the others.

Providers acknowledge that a majority of patients with comorbid alcohol use disorders have medical conditions that are either caused or affected by their on-going use of alcohol and some even have legal repercussions from use. When medications are prescribed, providers have had very positive experiences indicating patients tend to maintain sobriety longer, have less legal problems, and are better able to engage in their medical and psychiatric care.

Screening for alcohol use disorders with tools such as the AUDIT is avoided, with almost half of the providers reporting never having used it, a trend also seen amongst providers associated with chemical dependence facilities Figures 1-3.

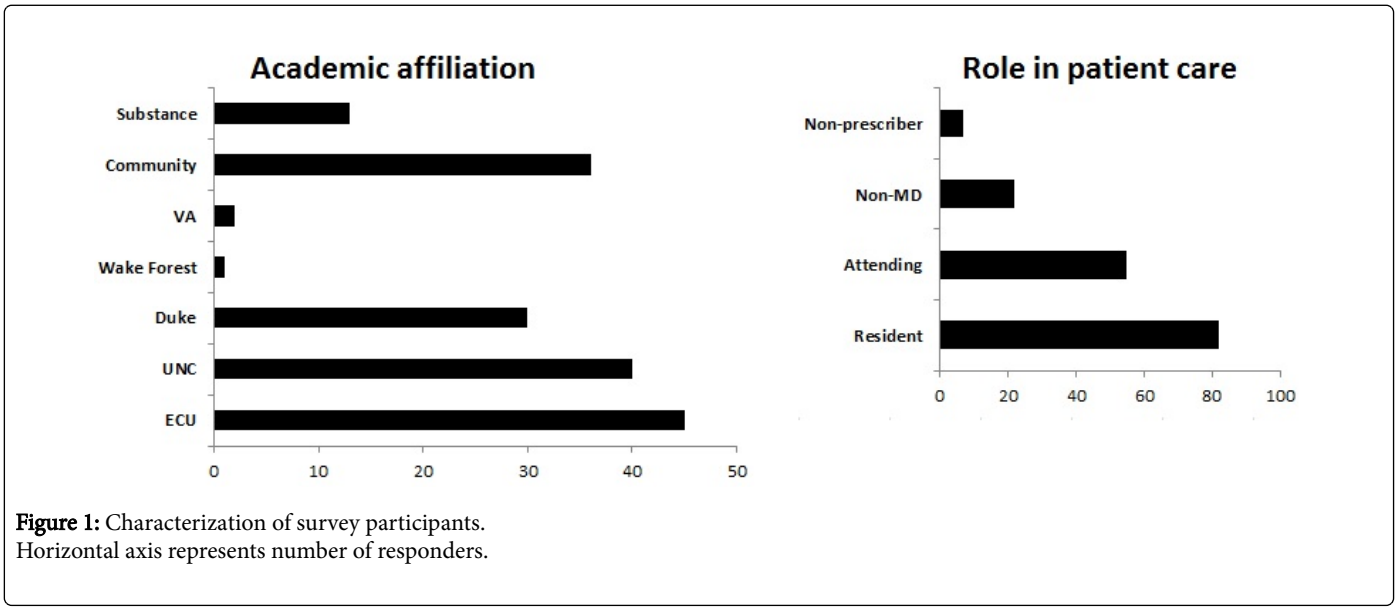

Figure 1: Characterization of survey participants.
Horizontal axis represents number of responders.

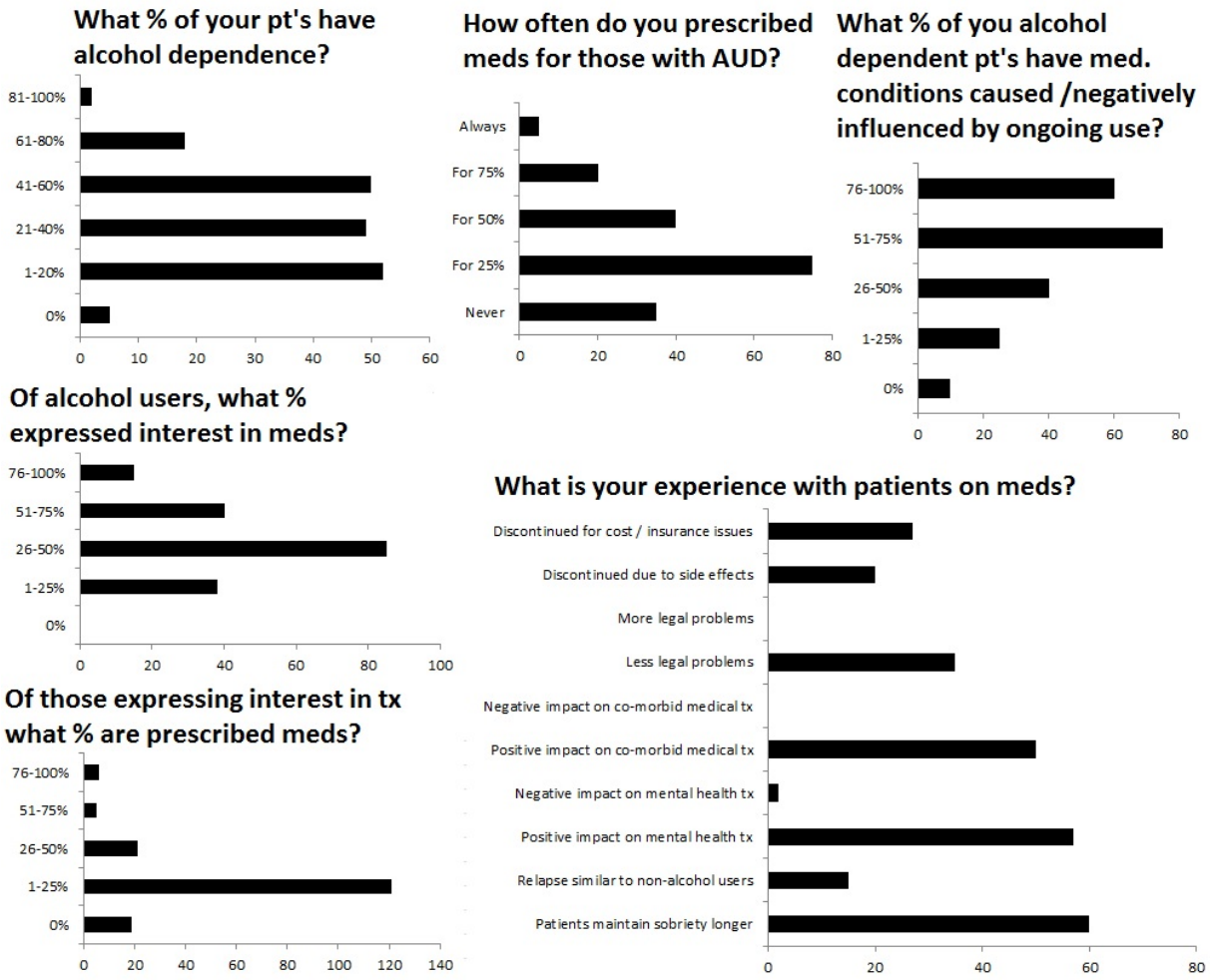

Figure 2: Alcohol use disorders in general psychiatric patient population, impact on health, and influence of pharmacotherapy introduction. Horizontal axis represents number of responders.

Limitations

This study sampled a relatively wide variety of providers and settings within the boundaries of North Carolina. The numbers of Veterans Affairs participants were not significant and hence no interpretations can be made regarding their practices. Whether there is generalizability of the practices of nationwide providers cannot be confirmed. The number of responders participating is relatively low, however, the high response rate increases the validity.

Summary and Conclusion

Alcohol use disorders are highly prevalent, highly comorbid disabling disorders that often are untreated. Treatment guidelines recommend FDA approved medications in conjunction with psychosocial interventions. The data gathered indicates prescribers avoid pharmacotherapy due to lack of comfort and knowledge. We hypothesized there would be financial barriers in a current alcohol treatment system that is traditionally non-medically oriented. However, analysis does not indicate this is the case. Although it is recommended to start with FDA approved medications, off-label use is high. Despite the positive implications noted when medications are instituted, providers' ambivalence continues. Screening with recommended standard instruments such as the AUDIT, although poorly utilized based on our findings, would better identify those at high risk and those with established AUD. This suggested that there exists a pattern of missed opportunities to facilitate discussion about treatment.

As part of our daily practices, general psychiatrists should consider gaining confidence in using evidence-based, FDA approved, medications in treatment of AUDs. In those with concurring mental disorders increased use of psychotropics could substantially improve the efficacy of treatment. In the treatment of alcohol use, medications seem avoided by most providers. There is a substantial opportunity for improved outcomes of care for AUD with focused education about medication-assisted approaches.

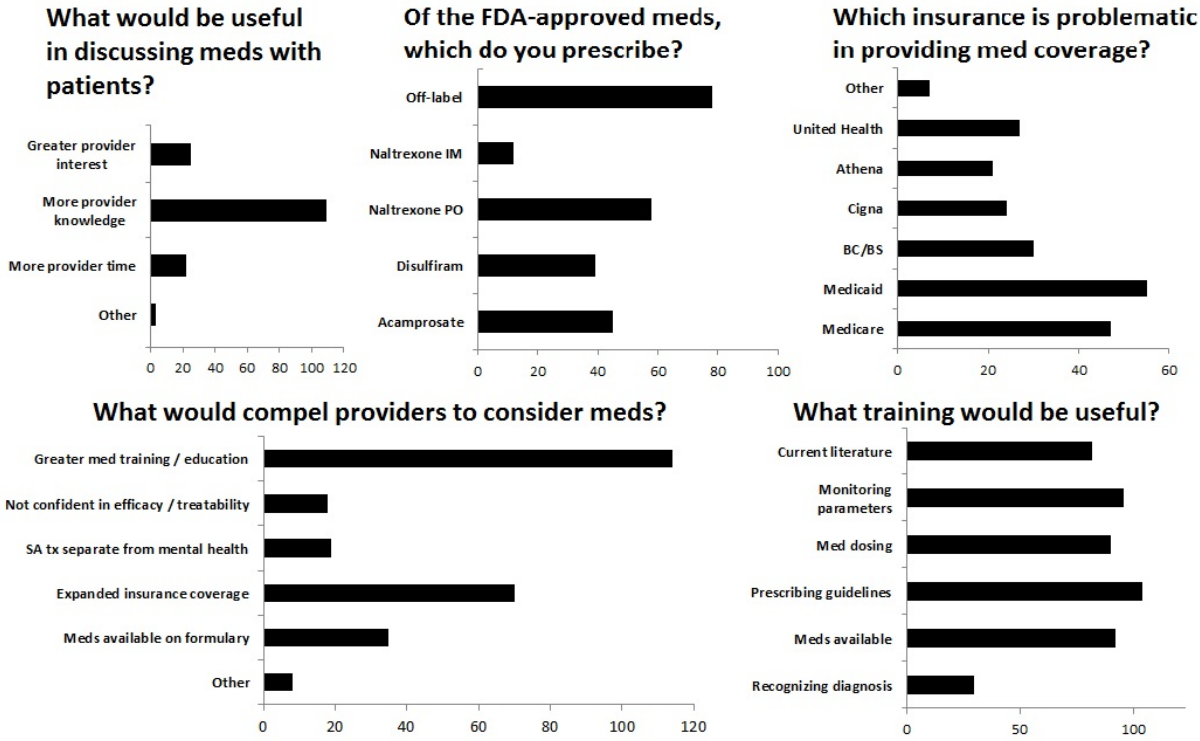

Figure 3: Trends of prescribing and elements guiding prescriptions. Horizontal axis represents number of responders.

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