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Practical implementation of varenicline as an aid to smoking cessation in clinical practice

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REZUMAT

Implementarea în practică a vareniclinei în terapia de renunțare la fumat

Vareniclina este un medicament care nu conține nicotină, conceput și dezvoltat ca un mijloc terapeutic venind în ajutorul celor care încearcă să renunțe la fumat și reprezintă cea mai nouă clasă de medicamente aprobate pentru terapia renunțării la fumat, după terapia de substituție nicotinică și bupropion. Vareniclina poate fi prescrisă atât pacienților care nu au încercat niciodată medicamente pentru renunțarea la fumat, cât și celor la care alte mijloace terapeutice nu au avut succes. În practică este recomandată implementarea terapiei de renunțare la fumat cu vareniclină.

***Cuvinte cheie**: vareniclină, abandonul fumatului, adjuvant non-nicotinic*

ABSTRACT

Varenicline is a non-nicotinic medication developed as an aid for people who are trying to stop smoking and is the third class of drug, after nicotine replacement therapy and bupropion, to be approved for smoking cessation. Varenicline can be prescribed as a treatment for patients who have never tried medication for smoking cessation as well as for those in whom other treatments have not been successful. Practical suggestions are made for implementing smoking cessation with varenicline.

***Key words:** varenicline, smoking cessation, non-nicotinic aids*

History

Nicotine binds to various subtypes of nicotinic acetylcholine receptors, both peripherally and in the central nervous system. The receptors are ligand-gated ion channels. Binding of nicotine allows the channels to open, allowing the entry of cations, including sodium and calcium and depolarization. This leads to the release of a variety of neurotransmitters, most notably, dopamine. Addiction is linked strongly to the binding of nicotine to α-4 β-2 nicotinic acetylcholine receptors in the ventral tegmental area causing the release of dopamine in the nucleus accumbens[4,5]. This discovery led to the idea that a partial agonist or an antagonist to the receptor could lessen the symptoms of nicotine withdrawal and antagonize the rewarding effects of nicotine.

Scientists at the pharmaceutical company Pfizer started to develop such a medication in the early 1990's based in part on the structure of cytisine[8]. Cytisine, an alkaloid that is found in certain plants, has been used in some countries in central Europe as a substitute for nicotine and was shown to have weak partial agonist activity at nicotinic receptors. After several years of development varenicline was synthesized by modifications to benzazephine, a substructure of cytisine[8]. Varenicline is a partial agonist of the α-4 β-2 nicotinic acetylcholine receptor and displays high selectivity to the α-4 β-2 nicotinic acetylcholine receptor compared to other subtypes. Varenicline has about 40-60% of the efficacy of nicotine in stimulating dopamine release in the brain in animal models[34]. As a partial agonist varenicline reduces the usual nicotine-induced dopamine release to the level of varenicline alone (nicotine is blocked).

The medication was approved for smoking cessation initially in the USA in 2006, and subsequently in over 80 countries. It is considered to be an effective and safe option for medical treatment of addiction to cigarettes[19-21].

Mode of action, pharmacokinetic characteristics and dosage

The agonist action of varenicline is thought to partially replace the rewarding effects of nicotine during smoking abstinence, while the antagonist action partially blocks the reinforcing effects of nicotine, i.e. feeling of reward, satisfaction with the cigarette and enjoyment of respiratory tract sensations during lapses to smoking. Studies have shown that varenicline reduces craving and the rewarding effects of smoking after the target quit date to a greater extent than bupropion[40] and than nicotine patches[2].

The half-life of varenicline is ~ 24 hours and the C_{max} is reached within 3–4 hours. Steady state is reached within 4 days. There is no effect of food on blood concentrations of varenicline. Varenicline undergoes minimal metabolism with >90% excreted unchanged in urine and <10% as metabolites[1]. Renal excretion is the primary mode of clearance. Patients with impaired renal function should be given a lower dose of varenicline (1 mg daily). Varenicline is not recommended for patients with end-stage renal disease. No dose adjustment is needed for patients with liver disease. No

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clinically meaningful drug-drug interactions have been described[32].

The recommended dose of varenicline is 1 mg twice daily. The smoker starts taking varenicline at least 1 week before stopping smoking. In the first week of administration, the dose is gradually increased from 0.5 mg once daily on days 1 through 3, 0.5 mg twice daily on days 4 through 7, and then 1 mg twice daily on day 8 and onwards. Day 8 (1 week after starting therapy) is usually the target quit date. Because the therapeutic dose is only reached on the target quit date, it may be advisable for some patients to delay the quit date until a steady state of the 1 mg twice daily dose has been reached, i.e. on day 12 or up to day 14 after the drug is initiated. This dose adjustment period reduces nausea compared with starting the full dose at once[30]. The recommended duration of treatment is 12 weeks.

Clinical studies

Nine randomized placebo-controlled clinical trials of smoking cessation with varenicline have been reported to date[15,22,27,30,41,26,25,39,42] as well as an additional relapse prevention study[38]. Of these, one was a dose finding study[27] and one was a titration study[30]. Three studies recruited smokers from Asian populations[25,39,42].

Two clinical cessation trials were identically designed double-blind, placebo-controlled studies in which smokers interested in quitting were randomly assigned to varenicline (1 mg twice daily), bupropion or placebo for 12-weeks[15,22]. Throughout this treatment phase subjects in both groups were followed weekly or biweekly and given motivational and behavioral support. Continuous abstinence from smoking was measured at 52 weeks. A meta-analysis pooling these four studies found an odds ratio of 3.2 (95% confidence interval 2.4-4.3) for continuous abstinence at week 52[7]. In absolute terms, the US guidelines metaanalysis found a 6-month quit rate of about 33% for varenicline and a 13% quit rate for placebo[13].

In one study, smokers were allowed to titrate varenicline from 0.5 to 2 mg daily during weeks 2-12 of treatment[26]. Quit rates at the end of 12 weeks of treatment were about 40% in varenicline-treated subjects versus about 12% in placebo-treated subjects. Varenicline-treated but not placebo-treated subjects tended to taper down their dosage over time. In a trial designed to test long term safety, smokers were assigned to varenicline or placebo for 52 weeks in a 2:1 ratio. The 7-day point prevalence was 37% versus 8% at week 52[41].

Prevention of relapse in patients who have quit smoking with varenicline

Smokers recruited to a clinical trial were treated with varenicline for 12 weeks[38]. Subjects who achieved abstinence for the last week, or longer, were then randomly assigned to varenicline for a further 12 weeks, or to placebo for 12 weeks, and all were followed for 1 year. The continuous abstinence rates from weeks 13 to 24 and weeks 13 to 52 were significantly higher for varenicline than for placebo (odds ratio at 24 weeks 1.8; odds ratio at 52 weeks 1.3, 95% confidence interval 1.1-1.7) and the 52-week quit rates were 44% for varenicline-treated subjects versus 37% for placebo-treated subjects.

Adverse events

The most common side effect of varenicline is nausea, experienced by about 30% of subjects in clinical trials and reported by nearly double this number in a real world setting[18]. Other side effects are disturbed dreams, insomnia, headache, flatulence, dyspepsia, constipation and change in taste. These events generally occur early in the course of treatment and are often reduced afterwards. Women seem to report symptoms more frequently than men, but in one study, did not discontinue treatment at higher rates than men[18]. Discontinuation rates of varenicline in clinical studies were only a few percentage points higher than placebo.

Neuropsychiatric adverse events

Based on post-marketing reports, the Federal Drug Administration in the United States, followed by drug authorities in other countries where varenicline is approved, issued warnings about serious neuropsychiatric symptoms in people taking varenicline or who had stopped taking varenicline. The symptoms include changes in behavior, agitation, depressed mood, suicidal ideation and attempted and completed suicide. More research is needed to determine whether these symptoms are due to the drug, to nicotine withdrawal, or have other causes[19,20]. Neuropsychiatric events were very rarely reported in clinical trials, however, the smokers included in clinical trials were probably healthier than smokers seen in usual clinical practice.

In 2008 the Institute for Safe Medication Practices, a nonprofit consumer surveillance organization issued a report indicating that serious adverse events associated with varenicline were more common than what was previously thought to be the case. As has been noted, the report failed to consider the number of users and that in about two thirds of all reported serious adverse events other medications were involved, especially psychoactive medications[21]. All patients prescribed varenicline should be monitored for adverse symptoms, especially neuropsychiatric ones.

Weight change after smoking cessation with varenicline

In the two identically designed trials[15,22] weight gain among participants who completed the treatment period and did not smoke during weeks 9-12 was 2-3 kg in varenicline-treated participants about 2 kg in bupropion-treated participants and about 3 kg in placebo-treated participants. No studies have indicated whether dietary change or increased exercise should be recommended to avoid the small weight gain, but this may be done according to the clinician's experience and judgment.

What is the role of varenicline in smoking cessation?

Because there are only three classes of drugs available to aid people who are making a quit attempt, most patients should be offered any of these classes of drugs to increase their chances of success on a given quit attempt. Varenicline can be prescribed as a treatment for patients who have never tried medication for smoking cessation as well as for those in whom other treatments have not been successful. If the patient relapses, as occurs most commonly, another class of drug may be tried.

Many patients under a physician's care will often have tried nicotine replacement therapy without prescription and on their own in previous quit attempts. Nicotine replacement therapy may be tried again, in adequate doses, combining two or more forms, and for a recommended period of time, but

seems to be less effective in some cases when tried the second time around[37]. Additionally, many patients wish for another approach than what they have tried previously. This leaves two medications, bupropion and varenicline, both of which require a prescription and follow-up at least for the course of treatment. As noted earlier, it is important that the smokers has confidence in the medication, and the patients' previous experience and preference should be taken into consideration in deciding which treatment to choose[3].

Varenicline is more effective than bupropion as shown by the pooled odds ratio (1.7; 95% confidence interval 1.3-2.2) of three studies where varenicline was compared head-to-head to bupropion[7]. Thus, a large number of smokers in a physician's practice will be candidates for the medication. The effectiveness of varenicline in a smoker who has successfully quit with varenicline previously, but relapsed, has not been studied.

In a head to head open label trial with nicotine patch, varenicline was more effective in the short term, but not after 52 weeks[2]. A limitation of this study was that the varenicline group began treatment 1 week before the target quit date whereas the group taking nicotine replacement therapy began treatment on the quit date. Among patients attending a tobacco dependence clinic in the United Kingdom who were receiving routine care, short-term cessation rates were higher with varenicline than with nicotine replacement therapy (odds ratio of 1.7; 95% confidence interval 1.1-2.7) but the incidence of adverse symptoms was higher in varenicline-treated than in nicotine-treated patients[35].

The initial office visit

All smokers that are seen in clinical settings should receive a brief intervention (ask about smoking, give brief advice, and give cessation support). If the smoker indicates that he or she is ready to make a quit attempt within a month or two, varenicline may be offered as an aid to the attempt. The physician should emphasize that the medication alone is not likely to be sufficient for long term success, and that motivation, behavior change and follow-up are required for optimal results. Smokers with cardiovascular or pulmonary disease, or other disease related to smoking, should strongly be encouraged to use medication, as both their risk from smoking and level of addiction are likely to be high. Varenicline is an appropriate medication for these patients.

At the initial clinic visit when a patient decides to make a quit attempt a quitting plan should be agreed upon between the physician and patient (Figure 1). The quit date should preferably be within a few weeks from the initial office visit, while motivation is presumably high. The date, or week for quitting that is chosen should be relatively free of interferences or situations that may make quitting difficult. These include parties, periods of high stress or vacations. Because varenicline needs to be started 1 week or more before the quit day, it may be useful to mark a calendar with the start of varenicline, quit date, and the end of varenicline 12 weeks after start (Figure 2). This gives the smoker a framework for the treatment course.

Clinical considerations in comorbid patient populations

In patients with a previous history of psychiatric disease, including but not limited to major depression, personality disorder, psychosis and substance abuse, assess whether the patient is likely to comply with the clinic appointments. Do not treat with varenicline if he or she is not likely to attend follow-up visits. Varenicline is not contraindicated in these patients, however close follow-up is important. While both bupropion and nortryptiline are antidepressants that work for smoking cessation, neither drug has shown greater efficacy for patients with a history of depressive disorders when compared to smokers without a history of depressive disorders[17].

In patients with current treated psychiatric disease, varenicline may be used and is not contraindicated. Follow-up should probably be scheduled weekly or at least biweekly. There have been case reports of exacerbation of psychiatric illness in patients with schizophrenia and bipolar disorder[14,23,24,31] while other case reports have not reported problems[12,29]. In a case series of 19 patients with schizophrenia who were on stable antipsychotic medication regimens, none were observed to experience psychotic relapse or significant worsening of psychiatric symptoms or side effects of antipsychotic medications[9]. None had a psychiatric hospitalization within 24 weeks of starting varenicline. A real life report from the United Kingdom found that the administration of varenicline to 107 subjects with psychiatric disorders did not exacerbate psychiatric symptoms, and that varenicline was equally effective in patients with or without mental illness[35]. Cigarette smoking accelerates the metabolism of many of the drugs that are used to treat psychiatric disorders[17]. When patients using these drugs stop smoking lower dosages may be adequate.

Patients with concurrent alcohol or other drug abuse should not be given varenicline. In frail persons, particularly women, consider using a lower dose of 1 mg of varenicline daily.

Patients who are highly nicotine dependent could possibly benefit from a higher dose of varenicline of 3 mg daily[11]. Tolerability of varenicline was shown to be acceptable following a single dose of 3 mg in smokers, while in nonsmokers there was decreased tolerability of this dose[10].

Follow-up

Considerable data show that follow-up, whether face-to-face contact[13], letters or telephone conversations[36] significantly increases cessation success rates. The schedule of follow-up in the published clinical studies has been quite intensive, with visits scheduled almost every week during the first 12 weeks of treatment. During a study visit, subjects in the trials are asked to fill out questionnaires, are asked about adverse events that may have occurred since the last visit, vital signs and carbon monoxide (CO) in expired air are measured and brief counseling is given. This model can be simplified in the usual real world clinical settings.

One model for follow-up is shown in Figure 1. The person trying to quit smoking is scheduled to see the physician 2-3 days after the quit date that has been agreed upon at the initial visit. This visit after 2-3 days is a key visit that allows the physician to assess any symptoms of nicotine withdrawal that the patient is experiencing. Also, the effect of varenicline and any side effects can be assessed early and addressed. Brief behavioral advice is given that addresses smoking triggers. Examples of issues that may come up at this visit and suggested interventions are given in Table I.

Some or all of the remaining visits up to week 12 may be done by telephone or scheduled with a trained nurse, allied

Table I.
Issues and interventions at the clinic visit 2-3 days after the quit date.

Issue	Intervention
The patient is smoking (same or reduced amount), but still wants to quit.	Set a new quit date about 1 week later and schedule follow-up 2-3 days after the new quit date.
The patient has reduced to 1-2 cigarettes per day.	Emphasize the importance of complete cessation. Discuss antecedents to smoking and how to deal with them. Ask the patient not to take a single puff for the next 2-3 days and schedule a new appointment to follow-up in 2-3 days.
The patient has not smoked, but does not feel that varenicline is helping with cravings, or does not feel any subjective effect of varenicline.	Emphasize that studies have shown that varenicline reduces urges and withdrawal symptoms, but this may differ among people. Discuss behavioral responses to cravings. Consider adding nicotine gum or other rapid-acting form of nicotine replacement therapy for cravings (this has not been tested in studies).
The patient feels agitated or has a change in behavior that started before he or she quit smoking, but after starting varenicline.	Assess the patient for suicidal ideation or behavior. If present, stop varenicline. If not present, schedule frequent clinic or telephone follow-up to reassess. Consider stopping varenicline and using nicotine replacement therapy for the quit attempt. Consider reducing varenicline to 1 mg daily.
The patient has nausea that is not helped by taking varenicline within 30 minutes of a meal or within 30 minutes of ingesting two glasses of water.	Consider prescribing an antiemetic or reducing varenicline to 1 mg daily.
The patient has disturbing dreams that have made it difficult to function at work the next day.	Provide reassurance, and emphasize that stopping smoking may involve some discomfort especially in the first 2 weeks or so. Ask the patient to call you for possible dose reduction if the symptoms are intolerable before the next appointment. Consider reducing the dose of varenicline to 1 mg daily if needed.
The patient feels that varenicline is effective and that though some cravings are present, they are not leading to smoking.	This is great! Because relapse to smoking is still very high during the first 2-3 weeks of a quit attempt, discuss situations that my lead to increased craving and how to deal with them.
The patient feels depressed, like „I've missing something" or „lost a friend".	Assess for suicidal thoughts or behavior. If present, stop varenicline. If not present, provide reassurance, emphasizing that depression is a symptom of tobacco withdrawal. Consider referral to psychiatric care if the patient meets criteria for major depression.
The patient feels that she or he has now quit smoking, and does not wish to continue on varenicline beyond the starting package.	Discuss that nicotine addiction upregulates brain receptors, and that the likelihood of relapse is very high. Encourage the patient to continue the plan made at the initial visit. Assess whether the cost of medication is a barrier and discuss costs in comparison to the cost of cigarettes.
The patient complains of irritability, and feels that he or she has undergone a change of personality.	Is the patient actually taking the drug? Discuss the time course of nicotine withdrawal, and that the symptoms usually last a short period of time, usually only up to 4 weeks. Discuss techniques of stress management. If there is a change in behavior consider stopping varenicline.

health professional, or smoking cessation behavioral counselor. A recent Cochrane metaanalysis[33] found reasonable evidence that counseling given by nurses is effective for smoking cessation, however, the effect may be weaker if the intervention is provided by nurses whose main roles is not health promotion or smoking cessation (suggesting the importance of specific training and orientation toward smoking cessation).

There is no need to monitor any clinical laboratory tests in patients taking varenicline. The drug has not been associated with significant hematologic, metabolic or other blood abnormalities and electrocardiogram monitoring is not needed.

In a real world setting, investigators found that subjects trying to quit smoking with varenicline who received any telephone counseling were less likely to discontinue their medication than those with Web support only[18].

Can varenicline be combined with other smoking cessation therapies?

The combination of varenicline with a nicotine patch is not recommended. In a small study, there was increased nausea with the combination[1]. Other combinations i.e. with nicotine gum, inhaler, or lozenge, or with bupropion, have not been studied. Using rapid acting nicotine replacement therapy, e.g. gum, inhaler or lozenge for cravings that appear despite varenicline treatment, is suggested by some clinicians.

Preventing relapse

The majority of smokers will return to smoking within one year after cessation. No behavioral therapies have been proven to reduce the risk of relapse. Even so, patients should be encouraged to identify their smoking cues and triggers and plan alternative coping strategies as part of their plan to quit smoking.

For patients who have responded to varenicline with at least 1 week of cessation at the end of treatment, a further course of 12 weeks of varenicline may increase 52-week quit rates[38]. A recent paper indicates that smokers who have not been continuously abstinent throughout the course of treatment may enjoy the greatest benefit of an extended course[16]. Table II suggests an approach to deciding whether to continue treatment at week 12.

Individual responsiveness?

Varenicline has shown similar effects in men and women, older and younger adult smokers, smokers with high or low dependency and people smoking 10 to <20 cigarettes/day, 20 to <30 cigarettes/day or 30 or more cigarettes/day[28]. Recent data has shown that there may be an association between nicotine dependence and the α-3, α-5, β-4 nicotinic receptor subunit genes on chromosome 15q25[6]; it is unknown whether these risk alleles predict response to varenicline (or other smoking cessation medications). Varenicline is not recommended in adolescents due to lack of research in this population.

Conclusion

Varenicline is a welcome addition to the limited number of options that physicians have available to aid smokers in stopping smoking. This article has described how to use the medication in clinical practice.

Table II.
Therapeutic considerations in patients who are smoke-free at the 12 week visit.

Immediate therapy with another 12 weeks of varenicline should be considered.
If the patient has been smoke-free since the target quit date, watchful waiting may be indicated. Varenicline may be restarted if withdrawal symptoms (especially craving) occur after a few days without treatment.
If the patient is smoke-free for at least a week, but has had 1 or more lapses since the quit date, continue varenicline for another period of 12 weeks.
Weaning to a lower dose of varenicline 1 mg every day may be done for smokers who are reluctant to continue a full course, and have had lapses.
At the 12-week visit, some patients will already have been without varenicline for some days or weeks, due to lack of compliance or scheduling considerations. Assess urges to smoke or cravings, and prescribe another 12 weeks of treatment if the patient appears to be at the verge of starting smoking.
Because some individuals treated with varenicline have reported neuropsychiatric disturbances after stopping varenicline, remind the patient to ask for medical help if suicidal ideation or behaviors develop.

Figure 1.
Algorithm showing treatment plan and follow-up

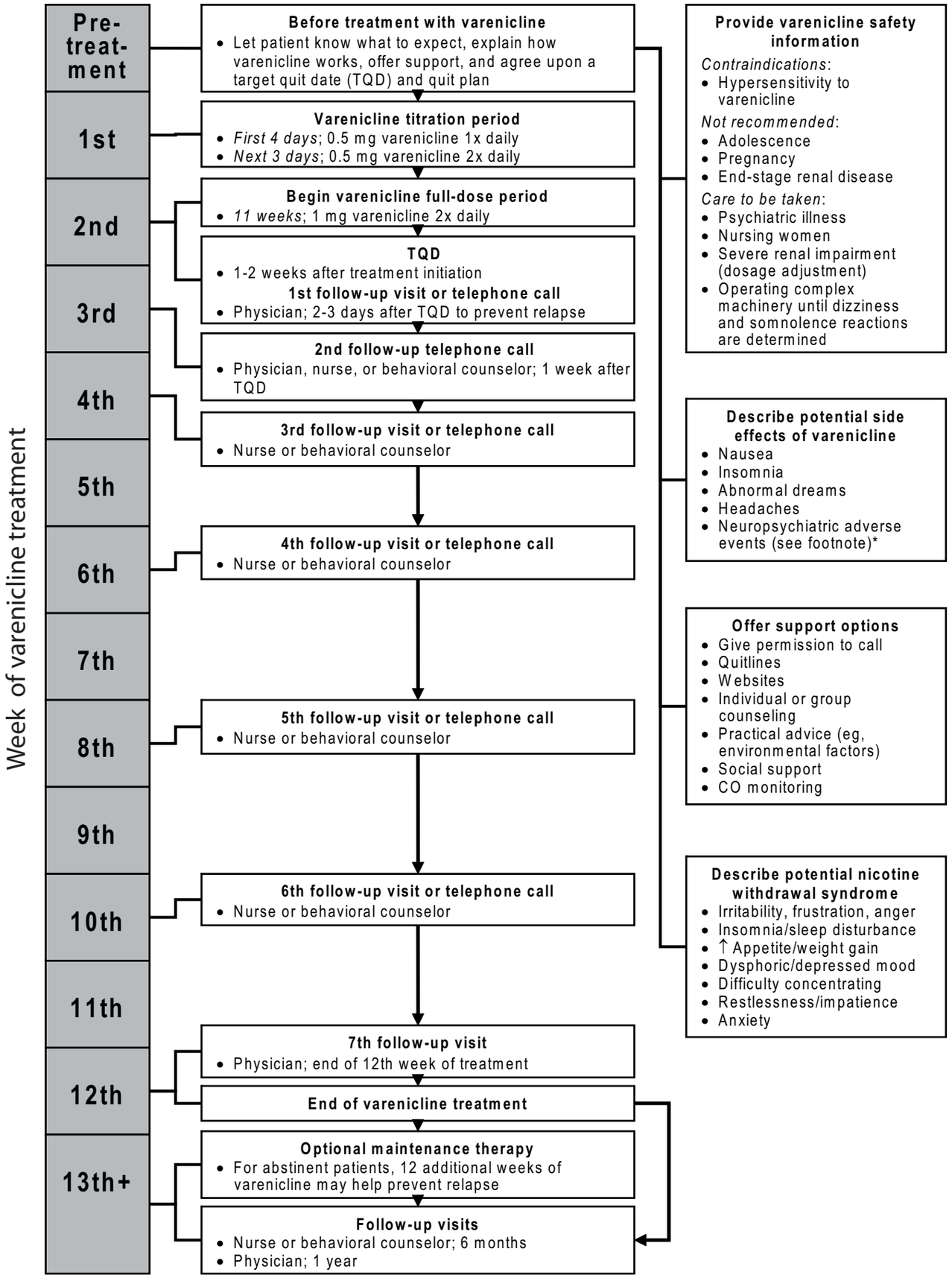
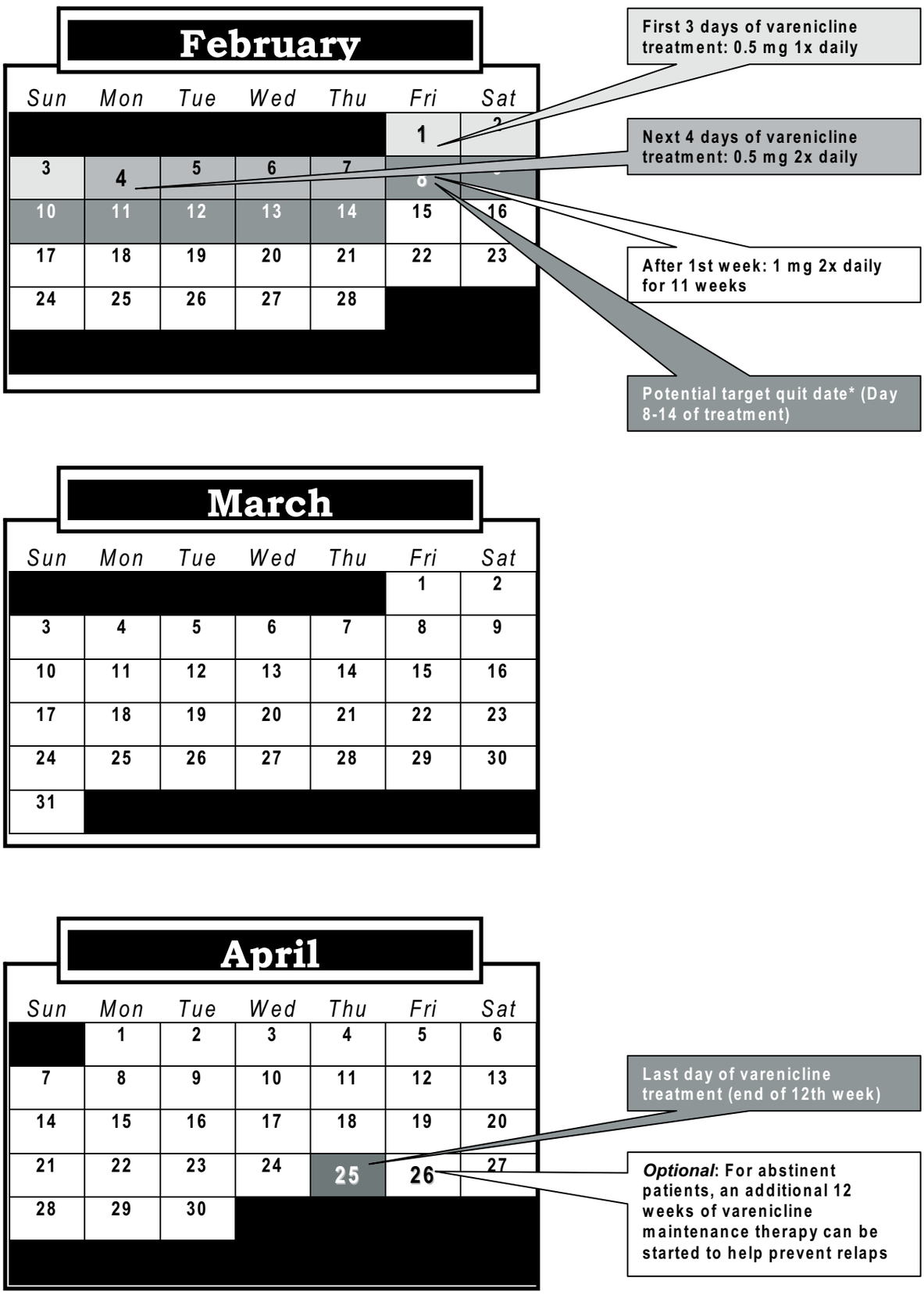


Figure 2.
Three-month calendar of treatment milestones with varenicline for smoking cessation.



* The target quit date (TQD) should be agreed upon between the physician and patient, but is recommended to occur during the 2nd week of treatment, when the varenicline dose increases to the therapeutic 1 mg twice daily.

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Conflict of interest statement: Serena Tonstad has received honoraria for lectures and consultancy for Pfizer, the manufacturer of varenicline.