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The Effect of Cytisine vs Varenicline on Smoking Cessation

To the Editor I have several comments about the recent trial comparing cytisine with varenicline.[1] First, caution must be exercised when stating that cytisine is definitively more effective than nicotine replacement therapy (NRT), as was stated in the abstract. This statement refers to 1 trial[2] that compared cytisine with varenicline but also allowed participants to use nicotine replacement monotherapy or any combination of nicotine patches, gum, or lozenges and did not report the usage of each of these potential regimens.

Second, even though the authors of the recent *JAMA* study[1] pointed out that standard cytisine dosing may not be optimal, they did not discuss the potential for dosing inconsistencies among participants. Although a strict dosing protocol is used for varenicline, cytisine dosing is based on the manufacturer's instructions of the specific brand used, which allows for flexibility in dosing. For instance, on days 17 through 20, instructions recommend taking 1 capsule every 5 hours during waking hours, with a maximum of 3 capsules daily. For days 21 through 25, 1 to 2 capsules may be taken daily. This flexibility exists throughout the entire cytisine dosing protocol and likely resulted in variability in dosing regimens among participants, thereby potentially influencing efficacy outcomes. In addition, the study protocol called for quit dates at day 5 for cytisine and at day 8 for varenicline. These different quit dates may have affected the outcomes by allowing either more time to adjust behaviors and develop coping skills prior to quitting or by providing more time to experience uncomfortable symptoms when using these medications and smoking a cigarette.

Third, the proportion of participants who discontinued treatment due to adverse events in this study[1] appeared twice as likely with varenicline compared with cytisine. A prior study showed that varenicline was approximately 1.5 times more likely to be discontinued due to adverse events than placebo.[3] It would be helpful to know the number of participants who discontinued treatment due to adverse events as well as the nature of these adverse events in this study.[1]

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In Reply Dr Lang raises some interesting points about our trial[1] comparing the effectiveness of cytisine vs varenicline for smoking cessation. At present, only 1 active comparator trial of cytisine vs NRT has been completed.[2] In this study,[2] cytisine was found to be more effective than NRT during follow-up at 1 week, at 1 month (primary outcome), at 2 months, and at 6 months after the quit day. Lang is correct that participants in this study could use single or combination NRT. They were provided a voucher to obtain an 8-week supply of nicotine patches (at varying strengths) and gum or lozenges (at varying strengths) or both gum and lozenges together at an additional cost.[2] The type and strength of NRT was determined based on participant preference and the recommendation of a quit-line advisor. Based on currently available evidence, cytisine appears more effective than NRT.[2,3] However, data from ongoing active comparator trials, which include NRT, will help determine the reproducibility of these findings.[4]

Our study[1] adopted the standard 25-day treatment regimen for cytisine, which sets the quit date at day 5 after initiation of the medication.[1,2] This quit date is justified on a pharmacological basis (ie, when the highest concentration of cytisine occurs in the blood).[4] The pharmacokinetics of varenicline differ; therefore, it has a different dosing regimen and different recommended quit date compared with cytisine. The standard dosing schedule of cytisine, which has been used for more than 5 decades and is recommended by manufacturers, may not be optimal.[4] Phase 1 and phase 2 studies of cytisine have not followed the typical path of drug development, unlike varenicline and NRT.[4] A simplified dosing regimen for cytisine with a more standard extended schedule may lead to enhanced treatment adherence and increased effectiveness but must be balanced against a tolerable adverse event profile. Although the results from a recent placebo-controlled trial and an active comparator trial of cytisine with amended dosing have shown some promise,[5,6] future studies may provide additional insights about revised treatment dosing of cytisine.[4]

The discontinuation rate of cytisine due to adverse events was reported in our article.[1] At 4-month follow-up, fewer participants reported treatment discontinuation in the cytisine group (16.5%) compared with the varenicline group (34.3%). Even though both the cytisine and varenicline treatment groups used standard dosing, their treatment durations differ, which must be considered when interpreting adverse event data.[1]

Cytisine is an effective and well-tolerated smoking cessation aid.[1-6] A relative lack of private investment has stifled production of and wider access to cytisine.[4] Future development of cytisine must occur with cost containment in mind because increased cost may risk or further delay the therapeutic potential of cytisine being realized more globally.

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Medical Debt in the US From 2009 to 2020

To the Editor The recent article about medical debt[1] found that the average stock and flow in medical and nonmedical debt have been declining over the last decade. However, we posit that ongoing changes in collection agency practices, debt reporting guidelines, and national consumer laws may obscure the true extent of medical debt in the US.

As described in the article's online Supplement,[1] debt in collections was defined as medical debt if it was not disputed by the consumer and if TransUnion classified it as medical debt.[2] The authors did not report the proportion of debt excluded from the analysis. The rates at which patients dispute medical and nonmedical debt could represent a confounder of both debt types. As a national credit reporting agency, TransUnion relies on how debt is classified by debt collection agencies and other furnishers of consumer credit data. The consumer data industry sets guidelines that govern how debt collections are categorized based on the creditor's type of business; however, access to these guidelines is limited to individuals actively involved in data furnishing or processing.[3] Even though the authors[1] noted that TransUnion's reports of medical debt may have differed from that of the other credit bureaus, aggregated data from any credit bureau may lack granular information needed to assess whether bills owed by patients to health care entities comprehensively represent medical debt.

The reported downtrends[1] in both the average stock and flow of medical debt also coincided with the passage of the Medical Debt Responsibility Act in 2013, which required national credit reporting agencies, including TransUnion, to remove paid medical collections from credit reports soon after they are paid.[2] The national credit reporting agencies cannot distinguish whether medical expenses are paid with cash, credit cards, or other financial products. Results from the Medical Bills Survey[4] found the proportions of households with outstanding medical bills that reported increasing their credit card debt, taking out other loans, or borrowing from payday lenders to be 34%, 15%, and 13%, respectively. Therefore, a substantial portion of both the stock and flow of medical debt reported by Dr Kluender and colleagues[1] may have been captured under nonmedical debt or may have been entirely excluded. Therefore, average medical debt in collections may not be declining. Any remaining downtrends in total debt in collections may be driven by changes affecting nonmedical forms of debt.

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In Reply Mr Uppal and colleagues note that our article[1] about medical debt in the US did not report the proportion of debt excluded because it was disputed by consumers. In June 2009, the first period of our study, 1.0% of medical debt and 2.9% of nonmedical debt was in dispute. In June 2020, the latest period of our analysis, 5.0% of medical debt and 9.7% of nonmedical debt was in dispute. Although we excluded disputed debt to avoid overstating the amount of debt in collections, including it would not have materially affected any of the study conclusions, including the relative increase in medical collections, debt concentration across geographies and income deciles, and divergent trends in medical debt in Medicaid expansion and nonexpansion states.

Second, Uppal and colleagues note that access to industry guidelines for classifying debt as medical are limited to