Difficult to swallow: patient preferences for alternative valproate pharmaceutical formulations

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Objective: To determine the degree to which swallowing valproate (VP) tablets is an issue, the proportion of patients who would prefer an alternative formulation, and the predictors of preference.

Methods: A quantitative telephone survey of eligible adults (n = 400, ≥18 years old) who currently take (n = 236) or previously took (n = 164) VP tablets within the past 6 months was conducted.

Results: More than half of the patients indicated that VP tablets were ‘uncomfortable to swallow’ (68.5%, n = 274) and were ‘very interested’ (65.8%, n = 263) in medications that were easier to swallow. When choosing conceptually between taking VP tablet once/day or an equally safe and effective but significantly smaller soft gel capsule twice per day, the 82.8%, (n = 331) preferred the soft gel capsule. In the multivariate regression analysis, perceiving soft gel capsules to be easier to swallow (OR = 73.54; 95% CI = 15.01 to 360.40) and taking VP more frequently (OR = 2.02; 95% CI = 1.13 to 3.61) were significant predictors of soft gel capsule treatment preference.

Conclusion: VP users would prefer a formulation that is easier to swallow, even if it is needed to be taken twice per day. When choosing between medications with similar efficacy and safety, physicians can consider patient preferences to optimize conditions for medication adherence.

Keywords: patient preference, valproate formulations, tablet characteristics

Introduction

Bipolar disorder, epilepsy, and migraine headache are prevalent and costly conditions for which valproate (VP) is often prescribed. Studies of US adults estimate bipolar prevalence at 3.7% to 5% with annual total cost estimates ranging from US$10 billion to US$45 billion.1-4 Epilepsy affects about 2.6 million Americans or just less than 1% of the general population, producing an estimated US$1.8 billion in direct medical costs and US$9.3 billion in indirect costs annually (1995 US$).7-9 Migraine headache is, by far, the most prevalent of these three disorders, affecting an estimated 17.2% of women and 6.0% of men in the US with the indirect costs to American employers estimated at approximately US$13 billion annually.10-13

Adherence with prescribed treatment is challenging for patients with these chronic mental and neurological disorders, which all require long-term medication adherence to optimize outcomes and reduce costs.14-20 Studies find that approximately half of patients diagnosed with bipolar disorder are either partially adherent or nonadherent to pharmacological therapy.21-23 Furthermore, 30% to 40% of bipolar patients who actively attempt to adhere to treatment are only partially successful.17
Estimates of treatment adherence among patients diagnosed with epilepsy were examined in observational studies finding medication noncompliance rates ranging from 59% to 71%. Adherence rates to pharmacologic pro-phylactic treatment for migraine headache was found to range from 35% to 64% in cohorts of adult Swedish migraineurs. Treatment nonadherence among patients with these conditions is likely to be a substantial contributor to unfavorable outcomes such as increased frequency of seizures and may consequently result in high direct and indirect health-related costs.

Given the significant impact of therapeutic adherence on outcomes and costs, health care providers must recognize that the patient is the end user and ultimate decision maker when it comes to taking medications and that patient satisfaction with a medication strongly affects that decision. While medication efficacy and safety are of utmost importance, characteristics such as tablet size, shape and ease-of-swallowing can affect patients' treatment preference and adherence. A study of patients with anxiety disorder found that significantly more patients preferred the capsule form of chlordiazepoxide as compared to the tablet form. A 2003 representative survey of US adults (N = 679) regarding difficulty swallowing pill-form medications found that approximately 40% of respondents had experienced difficulty swallowing pills. Among those having difficulty swallowing pills, the majority described feeling that it was 'stuck in the throat' (80%), having a 'bad aftertaste in the mouth' (48%), or 'gagging' (32%). This study supports the assertion that difficulty swallowing pills negatively impacts medication adherence, as it found that those reporting this problem also reported delaying doses (14%), skipping doses (8%), and discontinuing medication (4%) due to difficulty swallowing it. One in five adults surveyed reported the capsule form of a medication as compared to the tablet form. The survey contained 36 questions and took an average of 15 minutes to complete. The questionnaire was comprised of demographic questions, questions about perceived medication characteristics, medication use patterns, and preferences for medication characteristics (size, shape, and perceived ease of swallowing). In the univariate analyses of variance, chi-square and t-tests were used for categorical and continuous variables respectively. Multivariate logistic regression analyses were conducted to determine significant predictors of treatment preference. Variables that were statistically significant in the univariate analyses were included in the multivariate model. The dependent variable in multivariate analyses was 'Prefer Product X' ('yes' or 'no').

Methods
We conducted a quantitative telephone survey of adults (N = 400, ≥ 18 years old) who currently (n = 236) or previously (n = 164) took VP tablets (125 mg, 250 mg, or 500 mg) in the past 6 months. Participants were recruited using two different sources, a national on-line consumer survey panel and referrals from the National Association of the Mentally Ill. After the participant completed a short on-line survey to determine eligibility, qualified participants were invited to complete a structured interview about medication use, perceived pill characteristics, and medication preferences. A group of 14 telephone interviewers were rigorously trained to complete the survey according to nationally recognized marketing research standards. Prior to beginning the telephone interview, all participants were re-screened to ensure that they met the following eligibility criteria: ≥ 18 years old; took or have taken VP in the past 6 months; currently take or have taken VP for at least 2 months; took or have taken 500 mg VP tablet; have no member of the immediate household employed by or under contract for any pharmaceutical manufacturer (Figure 1). Informed consent was obtained through an online form. Respondents received an honorarium of US$35 to US$75 as a participation incentive (to enhance recruiting, the offered honorarium increased over time).

The survey contained 36 questions and took an average of 15 minutes to complete. The questionnaire was comprised of demographic questions, questions about perceived medication characteristics, medication use patterns, and preferences for medication characteristics (size, shape, and perceived ease of swallowing). In the univariate analyses of variance, chi-square and t-tests were used for categorical and continuous variables respectively. Multivariate logistic regression analyses were conducted to determine significant predictors of treatment preference. Variables that were statistically significant in the univariate analyses were included in the multivariate model. The dependent variable in multivariate analyses was 'Prefer Product X' ('yes' or 'no').

Results
Of 579 persons who initially responded, 400 were eligible to complete the telephone survey (Figure 1). More than half (56%) of survey respondents were between 35 and 54 years old with only 6% being younger than 24 years old and
only 1.2% being older than 65 years. Nearly two-thirds of respondents reported having <US$50,000 in annual household income. Of the respondents, 42% were married, 32% had never been married, and 22% were divorced. Overall, respondents were well-educated, with 67% reporting they had attended some college or had either a 2-year or 4-year college degree. Most respondents also had health insurance benefits, with over 75% reporting that all or most of their treatment costs were paid for by private insurance, Medicare, or Medicaid (Table 1).

The majority of respondents were prescribed VP to control bipolar disorder (n = 260, 65.0%). The remaining participants took VP primarily to prevent migraine headache (12.5%, n = 50), control epilepsy (11.8%, n = 47), or ‘other conditions’ (10.8%, n = 43). Respondents reported taking more than one VP tablet daily [mean (SD) = 2.5 (1.2) and 88.0% reported taking multiple other prescription medications daily [mean (SD) = 5.2 (3.6)] (Table 2).

Nearly half of the respondents discontinued taking VP as a result of the side effects they experienced (48.5%, n = 80), primarily weight gain (24.8%). In addition, slightly more than a third said that they stopped because it did not reduce their symptoms (35.2%, n = 58) (Figure 2). The majority of respondents reported their VP tablet was ‘uncomfortable to swallow’ (68.5%, n = 274) and were ‘very interested’ (65.8%, n = 263) or ‘somewhat interested’ (18.0%, n = 72) in taking a soft gel medication that appeared to be easier to swallow. When presented conceptually with a choice between taking

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**Figure 1** Participant screening process (initial sample size = 579).

**Note:** From the initial pool of 579 patients, 20 patients entered the survey but did not answer any questions, hence were excluded from the study.
Table 1  Respondent characteristics (N = 400)

| Characteristics               | Overall (N = 400) | Current VP users (N = 236) | Previous VP users (N = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| Age group                     |                   |                           |                             |
| 18–24 years                   | 24 (6.0%)         | 14 (5.9%)                 | 10 (6.1%)                   |
| 25–34 years                   | 84 (21.0%)        | 53 (22.5%)                | 31 (18.9%)                  |
| 35–44 years                   | 113 (28.3%)       | 64 (27.1%)                | 49 (29.9%)                  |
| 45–54 years                   | 111 (27.7%)       | 61 (25.8%)                | 50 (30.5%)                  |
| 55–64 years                   | 63 (15.7%)        | 39 (16.6%)                | 24 (14.6%)                  |
| 65 and Above                  | 5 (1.3%)          | 5 (2.1%)                  | –                           |
| Sex                           |                   |                           |                             |
| Male                          | 118 (29.5%)       | 92 (38.9%)                | 26 (15.8%)                  |
| Female                        | 282 (70.5%)       | 144 (61.1%)               | 138 (84.2%)                 |
| Marital status                |                   |                           |                             |
| Never married                 | 121 (30.2%)       | 74 (31.4%)                | 47 (28.6%)                  |
| Married                       | 174 (43.5%)       | 104 (44.1%)               | 70 (42.7%)                  |
| Divorced                      | 95 (23.8%)        | 49 (20.7%)                | 46 (28.1%)                  |
| Widowed                       | 9 (2.2%)          | 8 (3.4%)                  | 1 (0.6%)                    |
| Prefer not to answer          | 1 (0.3%)          | 1 (0.4%)                  | –                           |
| Annual household income       |                   |                           |                             |
| Less than $15,000             | 78 (19.5%)        | 45 (19.1%)                | 33 (20.1%)                  |
| $15,000–$29,999               | 93 (23.2%)        | 44 (18.6%)                | 49 (30.0%)                  |
| $30,000–$49,999               | 77 (19.2%)        | 49 (20.8%)                | 28 (17.1%)                  |
| $50,000–$69,999               | 59 (14.8%)        | 34 (14.4%)                | 25 (15.2%)                  |
| $70,000–$99,999               | 46 (11.5%)        | 34 (14.4%)                | 12 (7.3%)                   |
| $100,000 or more              | 36 (9.0%)         | 23 (9.8%)                 | 13 (7.9%)                   |
| Don't know/Prefer not to answer| 11 (2.8%)        | 7 (2.9%)                  | 4 (2.4%)                    |
| Education                     |                   |                           |                             |
| Some high school              | 10 (2.5%)         | 6 (2.5%)                  | 4 (2.4%)                    |
| High school degree or GED     | 62 (15.5%)        | 39 (16.6%)                | 23 (14.0%)                  |
| Some college                  | 148 (37.0%)       | 78 (33.1%)                | 70 (42.7%)                  |
| 2- or 4-year college degree   | 121 (30.3%)       | 69 (29.2%)                | 52 (31.7%)                  |
| Postgraduate work             | 58 (14.4%)        | 43 (18.2%)                | 15 (9.2%)                   |
| Prefer not to answer          | 1 (0.3%)          | 1 (0.4%)                  | –                           |
| Prescription insurance coverage|                 |                           |                             |
| Pay 100% out of pocket        | 28 (7.0%)         | 9 (3.8%)                  | 19 (11.6%)                  |
| Have insurance but pay significant costs out of pocket | 51 (12.7%) | 32 (13.6%) | 19 (11.6%) |
| Have insurance that pays all/most of costs | 178 (44.5%) | 113 (47.9%) | 65 (39.6%) |
| Have Medicare/Medicaid        | 142 (35.5%)       | 81 (34.3%)                | 61 (37.2%)                  |
| Other/don't know              | 1 (0.3%)          | 1 (0.4%)                  | –                           |

Abbreviation: GED, General Educational Development.

their current VP tablet once daily and taking a smaller, soft gel capsule (‘Product X’) with equivalent safety and effectiveness twice daily, the majority (82.8%, n = 331) preferred the soft gel capsule medication. An even larger majority of respondents (85.3%, n = 341) indicated preferring the soft gel medication when asked, ‘If both medications were available when you first began taking VP, which would you have preferred?’ (Table 3)

Univariate analysis of variance revealed that respondents preferring the soft gel capsule took VP tablets more times per day ($P = 0.05$) and were significantly more likely to: perceive that soft gel capsules were easier to swallow ($P < 0.001$);
Table 2 Valproate (VP) utilization patterns

| Utilization                                                                 | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|----------------------------------------------------------------------------|--------------------|---------------------------|----------------------------|
| **Primary reasons for taking VP**                                        |                    |                           |                            |
| Epilepsy                                                                  | 47 (11.7%)         | 29 (12.3%)                | 18 (10.9%)                 |
| Bipolar disorder                                                          | 260 (65.0%)        | 151 (63.9%)               | 109 (66.5%)                |
| Migraines                                                                 | 50 (12.5%)         | 32 (13.6%)                | 18 (11.0%)                 |
| Other                                                                     | 43 (10.8%)         | 24 (10.2%)                | 19 (11.6%)                 |
| **Type of VP (currently using or ever used)**                             |                    |                           |                            |
| Tablet form, several times per day                                       | 243 (60.8%)        | 133 (56.4%)               | 110 (67.1%)                |
| Tablet form, once daily                                                   | 266 (66.6%)        | 178 (75.4%)               | 88 (53.7%)                 |
| **Total milligrams of VP per day**                                        |                    |                           |                            |
| Mean (SD)                                                                 | 1176.38 (594.59)   | 1201.06 (574.36)          | 1140.85 (622.61)           |
| [Median]                                                                  | [1000.00]          | [1000.00]                 | [1000.00]                  |
| **Number of VP tablets per day**                                          |                    |                           |                            |
| Mean (SD)                                                                 | 2.46 (1.23)        | 2.53 (1.19)               | 2.37 (1.27)                |
| [Median]                                                                  | [2.00]             | [2.00]                    | [2.00]                     |
| **Times per day taking VP**                                               |                    |                           |                            |
| Mean (SD)                                                                 | 1.60 (0.70)        | 1.50 (0.67)               | 1.73 (0.73)                |
| [Median]                                                                  | [1.00]             | [1.00]                    | [2.00]                     |
| **Concurrent use of other prescription medications**                      |                    |                           |                            |
| Yes                                                                       | 352 (88.0%)        | 215 (91.1%)               | 137 (83.5%)                |
| No                                                                        | 48 (12.0%)         | 21 (8.9%)                 | 27 (16.5%)                 |
| **Total number of medications (including VP) daily**                      |                    |                           |                            |
| Mean (SD)                                                                 | 5.24 (3.63)        | 5.58 (3.68)               | 4.71 (3.51)                |
| [Median]                                                                  | [4.00]             | [4.00]                    | [4.00]                     |
| **Use of another medication for condition prior to VP**                  |                    |                           |                            |
| Yes                                                                       | 266 (66.5%)        | 153 (64.8%)               | 113 (68.9%)                |
| No                                                                        | 134 (33.5%)        | 83 (35.2%)                | 51 (31.1%)                 |

be female \( (P = 0.02) \); be married \( (P = 0.0001) \); and have a college degree \( (P = 0.006) \) than those preferring VP tablets. (Table 4) In the multivariate regression analysis, perceiving soft gel capsules as being easier to swallow \( (P < 0.001) \), taking VP more times per day \( (P = 0.02) \), and being currently married \( (P = 0.02) \) were significant predictors of soft gel capsule treatment preference (Table 5).

Respondents preferring the soft gel capsule to the tablet formulation did not differ by age, annual household income, or prescription insurance coverage (Table 4). Those preferring soft gel capsules to tablets also did not differ by primary reason for taking VP, total mgs of VP taken per day, number of VP tablets taken per day, concurrent use of other prescription medications, or whether they had treated the primary condition with another medication prior to taking VP (Table 4).

The respondents \( (n = 59) \) who preferred the VP tablet even if both medications had been available when they were initially prescribed VP, were asked to give specific reasons for this preference. The most common reason given was preference for a once daily dose (34.5%), followed by feeling that it ‘works well’ (27.6%), preferring a ‘name brand’ (8.6%), ‘don’t care’ (6.9%), ‘physician’s choice’ (6.9%), ‘don’t like gelcaps’ (6.9%), and ‘side effects’ (5.2%) (Figure 3).

The respondents \( (n = 341) \) who indicated preferring the soft gel capsule (had it been available when they were initially prescribed VP) were also asked to give specific reasons for this preference. The most common reason given was preference for a ‘smaller pill’ (61.2%), preferring an oral form that was ‘easier to swallow’ (55.1%), preferring a ‘soft gel’ (28.9%), feeling that it was ‘faster acting’ (8.8%), feeling
Figure 2 Reasons for discontinuing valproate (VP) (n = 164, multiple responses were accepted; only top responses are shown).

Table 3 Respondent perceptions and treatment preference

| Uncomfortable to swallow VP | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-----------------------------|------------------|---------------------------|-----------------------------|
| Yes                         | 274 (68.5%)      | 162 (69.6%)               | 112 (68.3%)                 |
| No                          | 126 (31.5%)      | 74 (31.4%)                | 52 (31.7%)                  |

Interest in taking a tablet that is easier to swallow

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| Very interested               | 263 (65.8%)       | 164 (69.5%)               | 99 (60.4%)                  |
| Somewhat interested           | 72 (18.0%)        | 41 (17.4%)                | 31 (18.9%)                  |
| Neither interested nor uninterested | 45 (11.2%)   | 22 (9.3%)                 | 23 (14.0%)                  |
| Somewhat uninterested         | 6 (1.5%)          | 2 (0.9%)                  | 4 (2.4%)                    |
| Very uninterested             | 14 (3.5%)         | 7 (2.9%)                  | 7 (4.3%)                    |

Appears to be easier to swallow

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| VP                            | 18 (4.5%)         | 11 (4.7%)                 | 7 (4.3%)                    |
| Product X                     | 382 (95.5%)       | 225 (95.3%)               | 157 (95.7%)                 |

Want to be made aware of Product X soft gel capsule

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| Yes                           | 312 (78.0%)       | 180 (76.3%)               | 132 (80.5%)                 |
| No                            | 88 (22.0%)        | 56 (23.7%)                | 32 (19.5%)                  |

Prefer if these medications were equal in effectiveness and side effects

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| VP                            | 69 (17.2%)        | 40 (16.9%)                | 29 (17.7%)                  |
| Product X                     | 331 (82.8%)       | 196 (83.1%)               | 135 (82.3%)                 |

Prefer if these medications were equal in effectiveness and side effects, and comparable in costs

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| VP                            | 63 (15.87%)       | 38 (16.1%)                | 25 (15.2%)                  |
| Product X                     | 337 (84.3%)       | 198 (83.9%)               | 139 (84.8%)                 |

Treatment preference

|                               | Overall (n = 400) | Current VP users (n = 236) | Previous VP users (n = 164) |
|-------------------------------|-------------------|---------------------------|-----------------------------|
| VP                            | 59 (14.7%)        | 36 (15.2%)                | 23 (14.0%)                  |
| Product X                     | 341 (85.3%)       | 200 (84.8%)               | 141 (86.0%)                 |

*Treatment preference was assessed using the following question: ‘If both these medications were available when you first started taking VP, which would you have preferred your doctor to prescribe?’
### Table 4  Treatment preference (univariate analyses)

| Variables                        | Treatment preference [N (%)] | P-value |
|----------------------------------|-----------------------------|---------|
|                                  | VP (N = 59)                 | Product X (N = 341) |
| **VP Users**                     |                             |         |
| Current                          | 36 (61.1%)                  | 200 (58.6%) | 0.73 |
| Previous                         | 23 (38.9%)                  | 141 (41.4%) |
| **Primary reasons for taking VP**|                             |         |
| Epilepsy                         | 7 (11.9%)                   | 40 (11.7%)  | 0.99 |
| Bipolar disorder                 | 39 (66.1%)                  | 221 (64.8%) |
| Migraines                        | 7 (11.9%)                   | 43 (12.6%)  |
| Other                            | 6 (10.1%)                   | 37 (10.9%)  |
| **Type of VP used**              |                             |         |
| VP immediate release             | 16 (27.1%)                  | 118 (34.6%) | 0.14 |
| VP extended release              | 30 (50.9%)                  | 127 (37.2%) |
| Both                             | 13 (22.0%)                  | 96 (28.2%)  |
| **Total milligrams of VP per day** |                          |         |
| Mean (SD)                        | 1222.46 (681.92)           | 1168.40 (578.90) | 0.52 |
| [Median]                         | [1000.00]                   | [1000.00] |
| **Number of VP tablets per day** |                             |         |
| Mean (SD)                        | 2.53 (1.35)                 | 2.45 (1.21)  | 0.66 |
| [Median]                         | [2.00]                      | [2.00]    |
| **Times per day taking VP**      |                             |         |
| Mean (SD)                        | 1.44 (0.68)                 | 1.62 (0.70)  | 0.05 |
| [Median]                         | [1.00]                      | [1.00]    |
| **Concurrent use of other**      |                             |         |
| prescription medications         |                             |         |
| Yes                              | 54 (91.5%)                  | 298 (87.4%) | 0.37 |
| No                               | 5 (8.5%)                    | 43 (12.6%)  |
| **Used another medication for**  |                             |         |
| condition prior to VP            |                             |         |
| Yes                              | 39 (66.1%)                  | 227 (66.6%) | 0.94 |
| No                               | 20 (33.9%)                  | 114 (33.4%) |
| **Appears to be easier to swallow** |                          |         |
| VP                               | 16 (27.1%)                  | 2 (0.6%)   | <0.001 |
| Product X                        | 43 (72.9%)                  | 339 (99.4%) |
| **Age group**                    |                             |         |
| 18–24 years                      | 3 (5.1%)                    | 21 (6.2%)  | 0.92 |
| 25–34 years                      | 12 (20.3%)                  | 72 (21.1%) |
| 35–44 years                      | 18 (30.5%)                  | 95 (27.9%) |
| 45–54 years                      | 18 (30.5%)                  | 93 (27.3%) |
| 55–64 years                      | 6 (10.2%)                   | 57 (16.6%) |
| ≥65 years                        | 2 (3.4%)                    | 3 (0.9%)   |
| **Sex**                          |                             |         |
| Male                             | 25 (42.4%)                  | 93 (27.3%) | 0.02 |
| Female                           | 34 (57.6%)                  | 248 (72.7%)|
| **Marital status**               |                             |         |
| Married                          | 18 (30.5%)                  | 156 (45.8%) | 0.0001 |
| Not married                      | 30 (50.9%)                  | 91 (26.7%) |
| Divorced/Widowed                 | 10 (16.9%)                  | 94 (27.5%) |
| Prefer not to answer             | 1 (1.7%)                    | 0 (0.0%)  |

(Continued)
that it would be ‘easier to digest’ (7.1%), and feeling that it would be ‘easier to store’ (5.3%) (Figure 4).

**Discussion**

Despite the fact that tablet-related characteristics, such as difficulties in swallowing tablets due to size and shape, seem to be a well-known problem among patients (negatively affecting their treatment acceptance and preference), few studies have addressed this issue. The finding from this survey-based study indicated that the majority of patients currently or previously treated with VP tablets reported difficulty swallowing them, is of interest due to its potential usefulness in improving clinical practice and patient outcomes. Results indicate that these patients are interested in knowing about medication with similar safety and efficacy that is formulated as a smaller, soft gel capsule. Given a choice between treatment with VP tablets or smaller, soft gel capsules with similar efficacy and safety, those who perceived the soft gel capsules to be easier to swallow would prefer treatment with that medication despite having to take it twice daily.

Many patients fail to voluntarily express important treatment preferences or barriers to adherence, such as difficulty swallowing medication during the clinical encounter. Data indicate that less than a quarter of people who have difficulty swallowing their pills discuss the problem with a health professional. The first nationally representative survey of pill-swallowing difficulty finds that only 14% of people who have difficulty taking oral medications indicate that their health provider has brought up the topic, and only 10% report initiating conversation about this difficulty themselves. While there are likely to be many contributing factors to this reluctance, it has been attributed to patients’ perceptions that physicians are focused on ‘treating numbers’ – a result of the increased emphasis on guideline-driven prescribing practices.

It is well documented that patient non-adherence to medication is a substantial barrier to the effective treatment of bipolar disorder, epilepsy, and migraine prophylaxis. However, data indicate that prescribing clinicians underestimate the extent of this problem. One study of medication adherence in bipolar patients (N = 429) found that although 57% reported missing all or some medication doses in the past 10 days, prescribing psychiatrists considered only 6% of these patients to be ‘treatment non-adherent’. There is a similar tendency to overestimate patient adherence with therapy among physicians prescribing for epilepsy treatment and migraine prophylaxis. Thus, for these

| Table 4 (Continued) |
|---------------------|
| Variables | Treatment preference [N (%)] | P-value |
| VP (N = 59) | Product X (N = 341) |
|-------------------|--------------------------|--------------------------|
| **Annual household income**<sup>a</sup> | | |
| < $30,000 | 27 (45.8%) | 144 (42.2%) | 0.34 |
| $30,000–$49,999 | 14 (23.7%) | 63 (18.5%) |
| $50,000–$69,999 | 5 (8.5%) | 54 (15.8%) |
| ≥ $70,000 | 10 (16.9%) | 72 (21.1%) |
| Don’t know/Prefer not to answer | 3 (5.1%) | 8 (2.4%) |
| **Education** | | |
| Some high school | 3 (5.1%) | 7 (2.1%) | 0.006 |
| High school degree or GED | 8 (13.6%) | 54 (15.8%) |
| 2- or 4-year college degree | 9 (15.2%) | 112 (32.8%) |
| Postgraduate work | 13 (22.0%) | 45 (13.2%) |
| Don’t know/Prefer not to answer | 1 (1.7%) | 0 (0.0%) |
| **Prescription insurance coverage** | | |
| Pay 100% out of pocket | 3 (5.1%) | 25 (7.4%) | 0.12 |
| Have insurance but pay significant costs out of pocket | 5 (8.5%) | 46 (13.5%) |
| Have insurance that pays all/most of costs | 21 (35.6%) | 157 (46.0%) |
| Have Medicare/Medicaid | 30 (50.8%) | 112 (32.8%) |
| Other/Don’t know | 0 (0.0%) | 1 (0.3%) |

**Notes:** P values in bold indicate significant at P < 0.05.

<sup>a</sup>US$. Abbreviation: GED, General Educational Development.
Table 5 Predictors of treatment preference (multivariate analysis)

| Variables                          | β estimate | Standard error | P-value | Odds ratio | 95% CI Lower CI | 95% CI Higher CI |
|-----------------------------------|------------|----------------|---------|------------|-----------------|------------------|
| Times per day taking VP           | 0.70       | 0.30           | 0.02    | 2.02       | 1.13            | 3.61             |
| Appears to be easier to swallow   |            |                |         |            |                 |                  |
| Product X                         | 4.29       | 0.81           | <0.001  | 73.54      | 15.01           | 360.40           |
| VP                                | –          | –              | –       | 1.00       | –               | –                |
| Sex                               |            |                |         |            |                 |                  |
| Female                            | 0.63       | 0.35           | 0.07    | 1.87       | 0.94            | 3.73             |
| Male                              | –          | –              | –       | 1.00       | –               | –                |
| Marital status                    |            |                |         |            |                 |                  |
| Married                           | 0.94       | 0.39           | 0.02    | 2.56       | 1.19            | 5.47             |
| Divorced/Widowed                  | 0.68       | 0.44           | 0.11    | 1.98       | 0.84            | 4.66             |
| Never Married                     | –          | –              | –       | 1.00       | –               | –                |
| Education                         |            |                |         |            |                 |                  |
| High school degree or GED         | 0.59       | 1.12           | 0.59    | 1.81       | 0.20            | 16.08            |
| Some college                      | –0.18      | 1.03           | 0.86    | 0.83       | 0.11            | 6.28             |
| 2- or 4-year college degree       | 0.68       | 1.07           | 0.53    | 1.98       | 0.24            | 16.29            |
| Postgraduate work                 | –0.33      | 1.06           | 0.76    | 0.72       | 0.09            | 5.76             |
| Some high school                  | –          | –              | –       | 1.00       | –               | –                |

Abbreviations: CI, confidence interval; GED, General Educational Development.

disorders, medication non-adherence could be a larger problem, making it critical to recognize the problems faced by the patients while taking medications, barriers to treatment acceptance, and factors affecting patient preference.

A supportive therapeutic alliance between patients and clinicians is known to improve patient adherence with treatment in the psychiatric and neurological disorders addressed here. An important opportunity exists for physicians to build the therapeutic alliance and potentially improve treatment adherence by engaging the patient in shared decision making regarding prescription medications. Studies of other medications further support the link between medication characteristics and adherence, finding that changes in oral medication formulation affect patient adherence to prescribed therapy. By engaging the patient in prescribing decisions and discussing factors that may improve adherence,
providers can optimize therapy to produce more effective management and greater improvements in the patient’s condition.29

The current study has several limitations. The US$35 to US$75 participation incentive that respondents received may have had effects on the results, though since it was not a focus of the study, the reasons cannot be explained. Similarly, additional analysis of marriage status, a statistically significant predictor of treatment preference, was not within the scope of the study. Most importantly, respondent demographics are not representative, thus, the results cannot be generalized to other populations. It is likely that reliance on the internet for initial patient recruitment accounts for the non-representative characteristics of our respondents including high proportions of young and middle-aged persons who were college educated and had health insurance coverage for prescription medications.

Time since VP cessation was not evaluated. It is possible that participants who stopped taking VP 6 months ago may have answered questions differently had they been asked nearer to when they took it.

Conclusions
The goal of any treatment is to offer an approach which eliminates or reduces the number and frequency of symptoms and produces the best possible quality-of-life while avoiding drug interactions and side effects. Given the significant impact of therapeutic adherence on clinical outcomes and health-related costs, providers must recognize the facts that patients make the ultimate treatment decision (that is to take medication as prescribed or not) and that patient satisfaction with a medication strongly affects that decision.29,30 In this study, users of VP indicated that they would prefer a formulation that is easier to swallow, even if it needed to be taken twice per day. This study provides preliminary data upon which further investigation should be based. Additional research is needed to clarify issues of patient medication preferences and to better quantify the impact of oral formulations that are easy to swallow and smaller in size on patient adherence with therapy.

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