

Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness

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ABSTRACT

Aims To compare the effectiveness of varenicline with nicotine replacement for smoking cessation and to evaluate the safety and effectiveness of varenicline in people with mental illness. **Design** Evaluation of consecutive routine cases before and after the introduction of varenicline. **Setting** National Health Service (NHS) tobacco dependence clinic in London, UK. **Participants** A total of 412 cases receiving routine care. **Intervention** Seven group support sessions over 6 weeks with either nicotine replacement therapy (NRT) ($n = 204$) or varenicline ($n = 208$). **Measurements** Verified abstinence 4 weeks after quit day, severity of withdrawal symptoms, incidence and severity of adverse drug symptoms, cost per patient treated and cost per successful short-term quitter. **Findings** Short-term cessation rates were higher with varenicline than NRT (odds ratio = 1.70, 95% confidence interval = 1.09–2.67). Varenicline was equally effective in those with and without mental illness. Craving to smoke, but not adverse mood, was less severe with varenicline than NRT. The cost per quitter was similar for varenicline and NRT. There was a higher incidence of adverse drug symptoms among those taking varenicline, but these were tolerated by most smokers. There was no evidence that varenicline exacerbated mental illness. **Conclusions** In this setting and with group support varenicline appears to improve success rates over those achieved with NRT, and is equally effective and safe in those with and without a mental illness.

Keywords Cost, craving, mental illness, nicotine replacement, smoking cessation, varenicline.

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INTRODUCTION

Varenicline (Champix/Chantix, Pfizer Ltd, Surrey, UK) is an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist licensed for the treatment of tobacco dependence by the USA FDA in May 2006 and by the European Agency for the Evaluation of Medicinal Products (EMA) in September 2006 [1,2]. The National Institute for Health and Clinical Excellence (NICE) for England and Wales recently recommended varenicline to the National Health Service (NHS) [3], based on the results of manufacturer-sponsored trials showing superior efficacy over placebo and bupropion (Zyban; GSK Ltd, Middlesex,

UK) [4–8]. Smokers with mental illness were excluded in these trials, and some have expressed concern about the safety and efficacy of varenicline in this substantial subgroup of smokers [9–11].

Nicotine replacement therapy (NRT) has become the standard pharmacological treatment for tobacco dependence, due to its well-proven effectiveness, benign side-effect profile and easy availability through pharmacy and general sales [12–14]. Without trials comparing varenicline with NRT, a key question as to whether clinicians should use varenicline in preference to NRT remains unanswered. Due to the large number of different NRT products and doses from which smokers currently choose

it is unlikely that a blind trial that reflects fully the potential of NRT will ever be conducted. To provide much-needed data on this issue we conducted an evaluation of the first varenicline cases in an NHS tobacco dependence clinic, using NRT cases treated immediately prior to the introduction of varenicline as a control cohort and adjusting comparisons for a comprehensive set of antecedent patient characteristics potentially prognostic for outcome. We were also able to assess the efficacy and safety of varenicline in those with mental illness.

METHODS

Patients and procedures

Patients attended the South London and Maudsley NHS Foundation Trust Specialist Tobacco Dependence Clinic as routine cases between May 2006 and April 2007. The treatment course comprised seven weekly group support sessions lasting 1–1.5 hours, plus NRT or varenicline. Smokers were booked consecutively into groups of between five and 25 depending on availability and preferred time. Throughout the evaluation period sessions were held at the same time of day (morning, afternoon or evening), with the same therapists and using the same procedures. The course required smokers to stop from the third session ('quit day') onwards, following assessment and preparation sessions in previous weeks.

At the first session ('assessment') a brief medical history was taken and the suitability of medicines assessed. In a group, smokers were then introduced to the clinic programme and the treatment options, as outlined previously in written material. At the end of the session patients were asked to decide, subject to contraindications, which medicine they preferred to take. Following the recommended schedule, those taking varenicline started treatment after the second group session ('preparation') and NRT treatment started 1 week later, immediately after group session 3 ('quit day'). Sessions 4–7 were designed to give support throughout the acute period of tobacco withdrawal symptoms, to dispense prescriptions and follow patients until 4 weeks after the quit day.

Treatments

Supported by advice from a clinician, those using NRT could choose between all licensed preparations and doses. During the period of this evaluation 60% used the nicotine patch, 25% used the nasal spray, 11% used the gum or lozenge and 5% used the inhalator or microtab. NRT was dispensed in three batches according to NICE guidance (2 weeks, 2 weeks, 8 weeks), with the last batch being dispensed at session 7 [13]. The clinic offered all patients a second NRT product to be used in combination with the first, although light smokers were discouraged

from excessive NRT use [12]. The second product was usually prescribed for about 6 weeks, or for 12 weeks at half the dose. Those taking varenicline were also given a 12-week course on four prescriptions (2 weeks, 2 weeks, 2 weeks, 6 weeks), with the last dispensed at session 7. Varenicline was introduced in the clinic at the beginning of January 2007, after which a minority of patients chose to use NRT. Before this the majority had used NRT, rather than bupropion. No patients were excluded from using NRT and only pregnant women (0), those breast feeding (0), those trying to conceive (1), those under 18 years old (2) and those with severe renal function impairment (3) were excluded routinely from using varenicline. NRT was dispensed under a Patient Group Direction by the clinic nurses and varenicline was prescribed by the resident doctor using FP10 NHS prescriptions. NHS prescription charge rules applied to all patients.

Materials and measures

Patients completed standard clinic materials. One week before the first session they were sent an appointment letter, an information sheet detailing the treatments and a self-completion questionnaire on demographics, smoking history, degree of tobacco dependence and medical history. The responses were reviewed with a clinician at the first session. At the start of sessions 2–7 patients completed a weekly report detailing smoking throughout the week, tobacco withdrawal symptoms and potential adverse drug reactions. They were then seen individually, where these reports were reviewed, and an expired-air carbon monoxide (CO) reading taken to measure any recent smoking.

Tobacco withdrawal symptoms and adverse drug reactions

The self-completion tobacco withdrawal symptoms scale consisted of seven known symptoms [15]. Each item was rated from 1 (not at all) to 6 (extreme). An adverse mood (negative affect) score was created as the mean response to the items: depression, irritability, restlessness and difficulty concentrating. A craving score was created from the items: difficulty stopping smoking, urges to smoke and strength of urges to smoke. Each week, patients were asked to report suspected adverse drug reactions using the question: 'If you used Champix, Zyban or Nicotine Replacement in the last week, please write below any unpleasant effects you think they may have caused'. When reported, the severity of each symptom was self-rated on a three-point scale: 1 = mild, 2 = moderate, 3 = severe.

Short-term smoking cessation outcome

To be classified as successful on the primary outcome measure ('CO-verified abstinence') participants had to report not smoking at all during the final 2 weeks of the course and record a CO level of less than 10 parts per million (p.p.m.) at the last session (session 7). As a secondary measure we also classified patients according to the Department of Health (DH) criteria ('DH Self-report abstinence'), as required of all NHS services [16]. Patients successful on this measure were those who were either 'CO-verified abstinent' or, if they did not attend session 7 for CO verification, could instead self-report abstinence via telephone or letter. Those who did not attend the last session and who failed to respond to telephone calls and a letter were classified as smoking [17]. All those reporting abstinence in person also passed CO verification in these cohorts.

Evaluation cohorts

The cohort sizes were selected to be sufficiently large to detect a difference between varenicline and NRT on the primary outcome measure. Because there are no published data comparing varenicline and NRT on which to base this, an estimate of the short-term relative efficacy of varenicline compared with bupropion was used instead [odds ratio (OR) = 1.83] [4,5]. This was considered an appropriate substitute given the similar efficacy of bupropion and NRT in meta-analyses [12,13,18]. Applying this ratio to the expected NRT cessation rate known from previous DH monitoring returns (about 60%) gave an expected varenicline cessation rate of 73%. With alpha set at 0.05 and statistical power at 0.8, cohorts of at least 200 per treatment would be required to detect the 13% projected difference. Only entire treatment groups were selected for evaluation, resulting in cohorts of 204 and 208 smokers treated with NRT and varenicline, respectively.

To achieve an evaluation cohort of at least 200 varenicline patients consecutive groups treated between January and April 2007 were included. The NRT cohort for comparison was chosen as consecutive groups treated immediately before the introduction of varenicline (May–November 2006). The small number using bupropion during this period were excluded. After varenicline was introduced 77% chose to use it. We excluded the 23% who did not wish to use varenicline and used NRT instead. A decision to undertake this evaluation was taken after the completion of patient treatment but before the clinical data had been analysed, following a request from the clinical service commissioners for an assessment of the cost implications of varenicline.

Data processing and statistics

Following usual practice, all data were entered on the clinic database for clinical, monitoring and evaluation report purposes. All patients gave signed consent for this at the first session. Smoking cessation rates and the incidence and severity of adverse symptoms were compared using the OR with 95% confidence intervals (CI), and logistic regression models were used to adjust for potentially confounding antecedent characteristics. To allow for possible group effects a beta-binomial model was used [19]. The severity of tobacco withdrawal symptoms were compared using the *t*-test, with adjustment using normal linear regression.

RESULTS

The varenicline and NRT cohorts were similar with respect to demographic, health history and smoking characteristics, apart from a higher proportion of patients of white European origin in the varenicline cohort (Table 1). In particular, there was no difference in confidence in stopping smoking, as self-rated after the medicine had been chosen but before it had been dispensed.

Smoking cessation

Varenicline versus NRT

Cessation rates were significantly higher with varenicline than NRT on both measures of short-term cessation, giving an estimated benefit of approximately 11% (Table 2). The effect of adjusting cessation rates for all the characteristics shown in Table 1 was marginal, slightly increasing the estimated relative effect of varenicline over NRT. The only characteristics prognostic of cessation in the multivariate model were: being older (more likely to stop), receiving state benefits (less likely to stop), smoking more (less likely to stop), having a smoking-related illness (less likely to stop) and smoking cannabis (less likely to stop). We also found no relation between the size of group in which a patient was treated and their likelihood of stopping.

When group success rates were considered as the unit of observation there was evidence that the group in which a smoker was treated had affected their likelihood of success as measured by DH self-report abstinence ($\chi^2 = 68.9$, $df = 44$, $P < 0.025$) but not according to CO-verified abstinence ($\chi^2 = 46.5$, $df = 44$, $P = 0.30$). Adjustment for the group effect using a beta-binomial model slightly increased the size of the confidence interval for DH self-report abstinence (OR = 1.92, 95% CI = 1.04–3.56, $\chi^2 = 4.68$, $P < 0.05$).

Table 1 Demographic, health and smoking characteristics of those taking nicotine replacement therapy (NRT) and varenicline.

	NRT (<i>n</i> = 204)	Varenicline (<i>n</i> = 208)
Demographics		
% Male	47.1 (69/204)	48.6 (101/208)
Age mean (SD)	44.6 (11.8)	45.4 (11.4)
% White European origin	69.1 (141/204)	78.8 (164/208)*
% No academic qualifications	30.4 (62/204)	30.3 (63/208)
% Receiving state benefits	56.4 (115/204)	58.2 (121/208)
Health		
% Current smoking-related disease	34.8 (71/204)	36.1 (75/208)
% Current mental health disorder	28.9 (59/204)	25.5 (53/208)
% Current drug or alcohol problems	5.4 (11/204)	5.8 (12/208)
% Currently smoking cannabis	18.6 (38/204)	16.3 (34/208)
% Drinking more than 21 alcohol units weekly	14.2 (29/204)	13.5 (28/204)
Tobacco smoking		
Number of daily cigarettes smoked mean (SD)	21.3 (10.5)	21.9 (11.1)
% Smoking within 5 minutes of waking	44.1 (90/204)	40.4 (84/208)
% Previously used NRT	73.0 (149/204)	79.3 (165/208)
% 'very' or 'totally' determined to stop	73.0 (149/204)	80.8 (168/208)
Confidence in stopping† (1–10) mean (SD)	8.0 (2.1)	8.1 (1.7)
% More than 3 attempts to stop in 5 years	21.6 (44/204)	27.4 (57/208)

*Difference $P < 0.05$. †Recorded at session 2, after medication known.

Table 2 Short-term smoking cessation rates in those taking nicotine replacement therapy (NRT) or varenicline.

Abstinence measure	NRT (<i>n</i> = 204)	Varenicline (<i>n</i> = 208)	Odds ratio (95% CI)	Adjusted odds ratio† (95% CI)	Difference (95% CI)
% CO verified*	61.3 (125/204)	72.1 (150/208)	1.63 (1.08–2.47)	1.70 (1.09–2.67)	10.8% (1.8% to 19.9%)
% DH self-report*	69.6 (142/204)	80.3 (167/208)	1.78 (1.13–2.80)	1.93 (1.18–3.17)	10.7% (2.3% to 19.0%)

*Four weeks after 'quit day'. †Adjusted for all characteristics shown in Table 1. CO: carbon monoxide; DH: Department of Health.

Table 3 Short-term smoking cessation rates in those taking single nicotine replacement therapy (NRT), combination NRT or varenicline.

Abstinence measure	Single NRT (<i>n</i> = 121)	Combination NRT (<i>n</i> = 83)	Varenicline (<i>n</i> = 208)	Odds ratio* (95% CI)	Adjusted odds ratio† (95% CI)	Difference* (95% CI)
% CO verified	57.9 (70/121)	66.3 (55/83)	72.1 (150/208)	1.88 (1.18–3.02)	1.96 (1.15–3.33)	14.2% (3.6%–25.0%)
% DH self-report	66.1 (80/121)	74.7 (62/83)	80.3 (167/208)	2.09 (1.26–3.47)	2.27 (1.27–4.05)	14.2% (4.2%–24.2%)

*Single NRT versus varenicline. †Adjusted for all characteristics shown in Table 1. CI: confidence interval; CO: carbon monoxide; DH: Department of Health.

Single-product NRT and combination NRT

Among the 204 patients in the NRT cohort, 121 (59%) used a single product and 83 (41%) used two products simultaneously. None of the characteristics shown in Table 1 were associated with whether single or combination therapy was used. For both outcome measures the observed cessation rates for combination NRT were higher than for single NRT therapy (Table 3). Varenicline was significantly more effective than single-product NRT

therapy and increased cessation rates by about 14%, equivalent to one additional success with varenicline for every seven smokers treated. However, there was no evidence of a difference in success rates between varenicline and combination NRT (OR for CO-verified abstinence = 1.32, 95% CI = 0.76–2.27 and OR for DH self-report abstinence = 1.38, 95% CI = 0.76–2.52). Adjustment for background characteristics only marginally altered this difference, increasing slightly the estimated advantage for varenicline.

Table 4 Short-term smoking cessation rates in those with mental illness.

Abstinence measure	NRT (<i>n</i> = 58)	Varenicline (<i>n</i> = 53)	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	Difference (95% CI)
% CO verified	55.2 (32/58)	71.7 (38/53)	2.06 (0.93–4.55)	2.88 (1.08–7.63)	16.5 (–0.01–34.2)
% DH self-report	65.5 (38/58)	81.1 (43/53)	2.26 (0.94–5.43)	3.07 (1.02–9.26)	15.6 (–0.00–31.8)

*Adjusted for all characteristics shown in Table 1, with the exception of mental illness. NRT: nicotine replacement therapy. CI: confidence interval; CO: carbon monoxide; DH: Department of Health.

Table 5 Tobacco withdrawal symptom scores.*

Measure	NRT (<i>n</i> = 136)	Varenicline (<i>n</i> = 156)	Difference (95% CI)	Adjusted difference‡ (95% CI)
Adverse mood score mean (SD)†	2.30 (1.00)	2.29 (1.04)	0.01 (–0.23–0.25)	0.04 (–0.20–0.28)
Craving score mean (SD)†	2.90 (1.15)	2.57 (1.06)	0.34 (0.08–0.59)	0.40 (0.14–0.66)

*In those attending the clinic 1 week after 'quit day' and recording a carbon monoxide reading of less than 10 parts per million. †Scored: 1 = not at all, 2 = slight, 3 = moderate, 4 = strong, 5 = very strong, 6 = extreme. ‡Adjusted for all characteristics shown in Table 1. NRT: nicotine replacement therapy; CI: confidence interval.

Mental illness

One hundred and eleven smokers (27%) reported that they were currently receiving treatment for mental illness (primary diagnosis: depression 64, bipolar disorder 14, psychosis seven, psychosis and depression 24, eating disorder two). In these patients there was a similar, or slightly greater, advantage for varenicline over NRT than seen in the whole group, although the confidence intervals were wide due to the reduced sample size (Table 4). Adjustment for background characteristics increased the size of the odds ratios slightly.

Tobacco withdrawal symptoms

Tobacco withdrawal symptoms self-rated 1 week after the start of the quit attempt, when severity frequently peaks, were compared between the NRT and varenicline cohorts [15]. To ensure that only those who could have potentially experienced withdrawal symptoms were included the analysis was restricted to those who had either stopped smoking completely or who had reduced their smoking sufficiently to record a CO level of less than 10 p.p.m. There was no evidence of a difference in experience of adverse mood, although craving severity was lower among those taking varenicline (Table 5). Adjustment for background characteristics did not affect this difference (difference = 0.40, $t = 3.04$, $P < 0.01$).

Adverse drug reactions

Symptoms reported significantly more by patients in either cohort are shown in Table 6. Compared with those using NRT there was a significantly higher inci-

dence of nausea, disturbed sleep, vivid dreams, drowsiness, constipation, headache, dyspepsia, dry mouth, bad taste, low mood, diarrhoea and disorientation in those taking varenicline (Table 6). Skin irritation (related to nicotine patch use) was the only reaction with a higher incidence in those using NRT. However, there was little evidence that when experienced, the severity of symptoms were different in the two cohorts, with the exception of anxiety/panic which was reported as either moderate or severe by all seven cases in the varenicline cohort.

Among the 208 patients who started their quit attempt using varenicline, seven (two with mental illness) switched to using NRT due to adverse symptoms. Six of these stopped smoking successfully. There was no evidence that adverse symptoms were experienced more in those with mental illness, or that when experienced, the symptoms were more severe (Table 6). There were no reports of mental illnesses symptoms being exacerbated by varenicline. Two reports were submitted under the Medicines and Healthcare Regulatory Authority monitoring scheme. One recent eye surgery patient experienced headaches and blurred vision and another patient had a severe psychological reaction likened to a 'bad LSD trip', including anxiety, paranoia, confusion and impaired motor control. Neither was hospitalized.

Cost

The average drug costs per patient treated and per successful quitter at 4 weeks were calculated. Single-product NRT treatment was costed at an average of £12 per week (£144 for a full 12-week course) and combination NRT therapy at an average of £18 per week (£216 for a full

Table 7 Drug costs for nicotine replacement therapy (NRT) and varenicline users (£).

	Single NRT (<i>n</i> = 121)	Combination NRT (<i>n</i> = 83)	All NRT (<i>n</i> = 204)	Varenicline (<i>n</i> = 208)
Cost per patient treated	99.2	169.6	127.8	136.8
Cost per quitter*	171.5	255.9	208.6	189.7
Cost per quitter†	150	227	183.6	170.4

*% Carbon monoxide (CO) verified abstinence. †% Department of Health (DH) self-report abstinence.

12-week course). Approximately 70% of those using NRT used products costing about £10 per week (mainly nicotine patches) and 30% used products costing an average of £15 per week. A second product was used on average for the equivalent of half a full 12-week course. Varenicline was costed at £13.65 per week or £163.8 per full 12-week course. The costs based on prescriptions dispensed are shown in Table 7. The mean cost per patient treated was slightly higher for varenicline than NRT overall, but the cost per short-term success was slightly lower.

DISCUSSION

A key question for clinicians treating tobacco dependence is whether to offer varenicline in preference to NRT. The published company-sponsored varenicline trials did not compare varenicline with NRT and hence did not provide a direct answer. Indeed, it would be extremely difficult to design a blind trial that reflects adequately the potential of NRT to be tailored to individual patients. In preference to an open-label trial with inherent potential bias we opted to undertake a comparative evaluation of routine varenicline cases using NRT cases treated immediately before the introduction of varenicline as controls. In so doing we were also able to assess varenicline in those with mental illness.

The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation. The magnitude of the benefit was similar to that seen for varenicline over bupropion in clinical trials with individual treatment. The results also indicate that varenicline is similarly effective in those with mental illness, supporting the regulatory decision to allow varenicline treatment in these patients. There was also evidence that the therapeutic benefit of varenicline over NRT may have been due, at least in part, to better control of urges to smoke, although there was no evidence of a difference on other withdrawal symptoms such as depression and poor concentration. We were able to adjust statistically all comparisons for a large number of antecedent characteristics, including the patient's confidence in success recorded after the treat-

ment was known to them. The integrity of these evaluation results is also supported by our observation of higher success rates with combination NRT therapy compared with single NRT therapy. The difference was close to that seen in randomized controlled trials [12]. Interestingly, we observed little difference between the efficacy of varenicline and combination NRT therapy, although this evaluation was not designed with adequate statistical power to test this.

Varenicline was associated with a number of adverse symptoms. Nausea and poor sleep/vivid dreams were the most common symptoms and were reported with a slightly higher incidence in these cohorts than in the manufacturer-sponsored clinical trials (nausea: 38% versus 29%) (poor sleep/vivid dreams: 43% versus 31%) [4,5]. The higher rate of sleep disturbance in this cohort may have been because of the high abstinence rate and because sleep disturbance is a recognized tobacco withdrawal symptom for many. Additional to the symptoms identified in the clinical trials we also observed a higher incidence of low mood, disorientation and diarrhoea, each experienced by 10 patients. Due possibly to either the moderate nature of these symptoms, the therapeutic effect of varenicline, or the supportive nature of the group treatment programme, the majority of symptoms were tolerated by the majority of patients and only seven (3%) switched to NRT after starting treatment with varenicline. We also found no evidence of more adverse symptoms being experienced by those with mental illness, although we cannot exclude the existence of other adverse symptoms with low prevalence.

Under the dispensing and prescribing schedule used the cost per patient treated was about 7% higher and the cost per short-term success was about 9% lower for varenicline compared with NRT. Other schedules, such as giving the full 12-week course on a single prescription, would lead to different costs. Given the extremely low cost of these treatments relative to the life-years they gain, such small differences are unlikely to make cost an important factor in prescribing decisions [13]. Although more effective compared with the single product NRT protocol usually advocated, varenicline was about 40% more costly per patient treated and about 11% more costly per successful short-term outcome. Again, this difference is

small enough not to be a major factor in commissioning decisions.

This evaluation had a number of limitations. Although all procedures, materials and staff were constant for NRT and varenicline cohorts and we were able to adjust for a variety of potentially confounding characteristics, there remains the possibility that unknown systematic factors biased the results. To our knowledge, no major taxation or legal changes occurred during the evaluation period to affect the likelihood of success. Perhaps a greater limitation is the fact that we had available only short-term outcome at the end of treatment, whereas tobacco cessation studies are now recommended to follow patients for at least 6 months [20]. However, comparative smoking cessation rates, as measured here by the OR, are usually highly stable over short- and long-term follow-ups [21], and our results are consistent with those from trials comparing varenicline with bupropion and trials comparing single NRT with combination NRT, all of which included 6- or 12-month follow-up.

There remain several other gaps in the varenicline evidence base in addition to those addressed here. Perhaps foremost is the question of whether varenicline is effective when prescribed by general practitioners without several sessions of expert group support or counselling, as given here, and in the company-sponsored trials and here, respectively. Without such support sessions there is the possibility that side effects might cause undue fear and a loss of confidence, leading to failure. A varenicline trial with routine brief general practitioner support is needed urgently.

DECLARATION OF INTEREST

J. S. and G. S. have acted as advisers to the manufacturers of nicotine replacement therapy and varenicline, for which they have received remunerations and hospitality, and have conducted smoking cessation trials with support from the manufacturers of nicotine replacement therapy. G. S. has given lectures on tobacco dependence sponsored by the manufacturers of nicotine replacement therapy and varenicline, for which she has received remunerations and hospitality. R. S. has given talks on smoking cessation sponsored by the manufacturers of varenicline, for which he has received remuneration. L. W., R. S. and A. M. attended the 2007 UK Smoking Cessation conference at the invitation of the manufacturers of varenicline. This evaluation was conducted without the involvement of any commercial organization.

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