

Table 1
Medications Used to Treat Neuropathic Pain in Our Patient Prior to Trial of Minocycline

Drug class	Medication(s)
NSAID	Ibuprofen, naproxen, aspirin, celecoxib
TCA	Amitriptyline, nortriptyline
SNRI	Duloxetine
GABA analogs	Pregabalin, gabapentin
Opioids	Tramadol, oxycodone
Topical pain medication	Topical lidocaine, topical capsaicin

Abbreviations: GABA, gamma-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug; SNRI, selective norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

Minocycline was tried as an alternative therapy for the patient's refractory pain. After 3 months of minocycline 100 mg twice daily, he reported subjective improvement of his pain symptoms, with objective improvement on autonomic function testing. Cardiovascular function normalized with autonomic function testing showing a normal heart rate response to deep breathing and normal blood pressure response to Valsalva maneuver, and quantitative sudomotor axon reflex testing was normal in his proximal and distal leg. At the time of the minocycline trial, the patient continued to take gabapentin, duloxetine, nortriptyline, and celecoxib. It is unclear whether the improvement was due to a combination effect of these medications with minocycline or due to minocycline alone.

There is increasing interest in the off-label use of minocycline as an alternative option for the treatment of pain and autonomic neuropathy. Studies have shown that minocycline is useful in preventing muscular pain hypersensitivity in human subjects⁵ as well as attenuating bone cancer pain⁶ and the development of diabetic neuropathy in rats.⁷ In a randomized, placebo-controlled study, minocycline was found to improve peripheral and autonomic neuropathy associated with type 2 diabetes.⁸

Several mechanisms have been proposed to link neuropathic pain with mast cells. Mast cells in the central and peripheral nervous system are involved in neuroinflammation and the development of neuropathic pain,⁹ especially those in close proximity to nociceptive C-fibers.¹ Mast cells release mediators including histamine, serotonin, interleukin-1 β , tumor necrosis factor- α , and interleukin-6, which can induce hyperalgesia, and mast cell-derived nerve growth factor can lower the threshold of nociceptor firing.¹ Mast cells also release substance P, which increases release of pro-nociceptive mediators, including leukotrienes and prostaglandins.¹

The exact mechanism by which minocycline affects the pain pathway and autonomic nervous system has not fully been elucidated, but is being studied in murine models.^{6,7} Minocycline reduces inflammatory cytokines and inhibits activation of microglia,¹⁰ cells involved in the pain pathway. Minocycline has also been shown to

inhibit spinal cord Notch signaling in rats with effects on the development of diabetic neuropathy.⁷

Our case demonstrates the successful use of minocycline as an alternative agent in the treatment of refractory neuropathic pain in the setting of underlying MMAS after treatment failure with typical pain medications. The case also highlights the potential challenges in managing neuropathic pain associated with MMAS, which will likely require a multidisciplinary approach to refine medication treatment options to improve quality of life in these medically complex patients. Although the case shows the promise of minocycline as an alternative pain agent, further studies will be necessary to validate its widespread use in patients with neuropathic pain. Further research is also needed to define the mechanisms involved in the development of neuropathic pain in patients with mast cell disorders.

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Face-to-face anti-tobacco intervention lowers cotinine level in asthmatic children

In this study we measured urine cotinine levels to assess the effectiveness of “face-to-face” intervention. The secondary end point was to assess the effect of anti-tobacco parental interventions on lung function in children with asthma.

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Patients were recruited to each study group until the number of parents or guardians of 70 children in each intervention group was reached. Inclusion criteria were children aged 6 to 18 years, with perennial asthma, with parents/guardians living in the same household and confirmed smokers. An environmental tobacco smoke exposure scale was created for the study based on data from the questionnaire (Table 1). Exposure to environmental tobacco smoke (ETS) was evaluated with a questionnaire addressed to parents/guardians and cotinine measurements in children's urine (based on



Table 1

Effects of Interventions in the Control and Active Groups Showing Within- and Between-Group Comparisons

	Before			After			P value ^a	P value ^b
	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile		
Control group								
CACT scale (points)	23	20	25	23	21	25	.13	.07
FEV ₁ (% predicted)	101.2	89.7	111.9	101.8	91.0	113.7	.93	.31
PEF (% predicted)	88.5	72.9	102.1	94.2	76.7	103.9	.40	.27
FeNO (ppb)	14.6	11.3	20.3	17.3	11.9	24.1	.15	.21
Cotinine level (ng/mL)	1.9	1.3	4.8	1.9	1.1	6.0	.08	.39
Exposure scale (points)	4.5	3	5	4	2	5	.02 ^c	<.001 ^c
Active group								
CACT scale (points)	23	19	25	24	21	26	.001 ^c	.06
FEV ₁ (% predicted)	100.0	92.7	112.0	102.4	96.7	112.8	.04 ^c	.31
PEF (% predicted)	84.4	69.6	98.6	87.1	82.2	99.1	.02 ^c	.27
FeNO (ppb)	17.9	14.3	25.3	18.9	14.3	25.1	.78	.21
Cotinine level (ng/mL)	4.3	2.4	11.7	2.9	1.1	8.9	.001 ^c	.39
Exposure scale (points) ^d	5	3	6	4	3	6	.001 ^c	<.001 ^c

Abbreviations: CACT, Childhood Asthma Control Test; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; SD, standard deviation.

^aWithin-group comparisons using the Wilcoxon test.

^bBetween-group comparisons using the Mann-Whitney *U* test.

^cStatistically significant (*P* < .05).

^dEnvironmental tobacco smoke scale used. For each mother and father: nonsmoker = 0; smoker, less than every day = 1; smoker, every day = 2; cigarette smoker, <10/day = 0; cigarette smoker, 10 to 20/day = 1; cigarette smoker, >20/day = 2; smoking at home is not allowed = 0; smoking at home is allowed but not everywhere = 1; smoking at home is allowed everywhere = 2; min: 0 point (the best); max: 10 points (the worst).

the Global Adult Tobacco Survey [GATS], which can be found at: <http://www.globaladulttobaccosurvey.org/?aspxerrorpath=/GATS/default.aspx/>.

The study protocol included 3 visits. At the first visit, children were assented and all parents or guardians of the patients provided oral and written consent and completed a questionnaire regarding smoking at home. Parents also received electronic peak flow meters for the children to monitor their lung function at home. The second visit was dedicated to an intervention. Asthma control was evaluated based on the Children Asthma Control Test (CACT), lung function was tested and exhaled nitric oxide (FeNO) was measured, and a urine sample was taken for cotinine measurement. The last visit took place 1 month after the second visit—with the same medical procedures being conducted at both visits.

The study was approved by the medical ethics committee, an institutional review board (IRB) of the Medical University of Lodz, Poland (approval no. RNN/76/14/KE).

On the first visit, parents were randomly divided into 2 groups of interventions. The control group included parents among whom only leaflets were distributed. The active group parents were individually re-educated about the harmful effects of ETS on their children, the source of tobacco smoke in the home environment, and methods of preventing children from exposure; they were given the same leaflets as the first group. Each “active” intervention took 20 to 30 minutes; an educator talked about the home situation of the child and other family members, taking into consideration smoking behaviors of smokers and other behaviors that could be linked with ETS exposure. Second, a PowerPoint presentation was shown to the parents, where all of the aforementioned topics were discussed. The last part was making a plan for the whole family to downsize ETS exposure. The plan aimed at modifying parents’ smoking behavior in their homes (eg, smoking outside their homes); all subjects received advice on how to quit smoking inside the home. This part of the study, including blinding of the patients, was performed by an educator. Urine sampling and lung function testing was performed by another person from the medical staff.

A urine sample was taken before the intervention and 1 month afterward. Urinary cotinine levels (in nanograms per milliliter) were obtained by employing a method described elsewhere.¹ Pulmonary function testing was done with a Master Screen unit

(Erich Jaeger GmbH, Hochberg, Germany) in accordance with guidelines of the American Thoracic Society/European Respiratory Society.^{2,3}

Patients were recruited to each study group until there were 70 children in each intervention group. Group sample sizes of 50 in each group achieved 92% power to detect non-inferiority using the one-sided Mann-Whitney *U* test, assuming that the actual distribution was logistic. The margin of equivalence in the cotinine level was −15 ng/mL. The significance level (α) of the test was .05. The data were drawn from populations with standard deviations of 20 ng/mL. A 20% drop-out rate was included. Wilcoxon and Mann-Whitney *U* tests were used for within- and between-group comparisons, respectively. All statistical computations were carried out using Stata release 12.1 Special Edition (StataCorp LP, College Station, Texas). *P* < .05 was considered statistically significant.

All patients were informed that resigning from the study will not influence their care in our public health outpatient clinic. A total of 101 patients and their caregivers completed the study—50 in the active group and 51 in the control group. Patients were excluded due to incomplete testing data (7 did not bring a urine sample, 10 were not able to perform spirometry), poor adherence (13 did not show up to the education lesson), or loss to follow-up (9 moved to another address). Within-group analysis revealed a significant decrease in cotinine level after the active intervention at *P* = .001 (Table 1). In the control group, there were no significant changes in cotinine level before and after the leaflet intervention (*P* = .08; Table 1); there was no difference between groups. Next, the cotinine level was dichotomized in the median value of cotinine reduction in the active intervention group (−0.92 ng/mL). Participants from both groups with cotinine reductions at or below −0.92 ng/mL were defined as responders. Only 14% of patients from the control group fulfilled the criterion. The selected group of active responders was included in further subgroup analysis.

In the control group, the analysis did not show any significant changes (*P* = .13) in the CACT after the intervention; an improvement in the CACT was seen after the intervention in the active group (*P* = .001; Table 1). Between-group analysis did not reveal any significant differences in changes in CACT scores.

There was no statistical difference in FEV₁ before and after the intervention in the control group (*P* = .93; Table 1). In the active

group, FEV₁ was significantly higher after the intervention ($P = .04$; Table 1). Between-group analysis did not reveal any significant differences in changes in FEV₁.

In the control group, peak expiratory force (PEF) analysis did not show statistically significant changes between before and after the intervention (Table 1). In the active group, we found a significant improvement in PEF measurements ($P = .02$; Table 1). Between-group analysis revealed no significant differences in changes in PEF.

Changes in FeNO results did not differ before vs after the intervention within groups, nor between groups (Table 1). In active responders, FeNO levels fell significantly after the intervention ($P = .01$).

The ETS exposure scale findings decreased significantly in the control ($P = .02$) and active ($P = .001$) groups; differences between groups were also statistically significant ($P < .001$) (Table 1).

According to our results, the face-to-face intervention among smoking families was effective and led to decreased ETS exposure and lowered cotinine levels in asthmatic children. Children whose parents passed the face-to-face intervention had better lung function and better asthma control than children in the control group. FeNO results did not change after the intervention in either group; however, FeNO levels dropped significantly in active responders. Limitations of our study include its small sample size and relatively short duration.

Several studies have recognized ETS as a risk factor that facilitates the development of asthma in children.^{3–5} The most significant results from our study indicate a change within the intervention group and a between-group difference on the exposure scale. The ETS exposure scale revealed that parents reported changes in smoking habits after both interventions, but the cotinine level fell significantly only in the active group. This result confirms that the effectiveness of any anti-tobacco intervention should

be evaluated with an objective parameter, such as cotinine measurements.

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Learnings from a pragmatic pilot trial of text messaging for high-risk adolescents with asthma



Clinical research with high-risk patient populations is complex because of economic burdens, lack of transportation, and so forth^{1,2}; therefore, conducting pilot studies before entering into a full-scale study is critical. Pilot studies can confirm the design and operational processes for a study³ and increase the likelihood of a successful clinical trial by identifying problems that may occur in the methods.^{4,5} Thus, we conducted a pilot study to identify issues in a research trial with low-income, publically insured, minority adolescents. Our study included multiple technologies that, without proper execution, could reduce the effectiveness of the intervention and the accuracy of the method by which the intervention was measured. Expected and unexpected challenges and the learnings that occurred shed light on issues faced in technology-dependent studies of high-risk adolescents.

We conducted a 5-month longitudinal, randomized text messaging intervention with high-risk adolescents who had long-term poorly controlled asthma. The inhaled corticosteroid (ICS) adherence monitoring and text messaging intervention was technology enabled and previously pilot tested.^{6,7} The intervention was designed to require few resources to enable replication in primary

care. We recruited 31 participants, which was smaller than anticipated because of our stringent criteria for long-term poor control and a change in insurance formularies mid-study, which drastically reduced the number of patients whose formulary ICS was compatible with the adherence monitor. Of the eligible patients approached, only a few declined.

Despite implementing quality control procedures developed by the real-time medication monitoring (RTMM) device company, there were challenges. A software update resulted in the loss of data, there were months in which no actuations were registered for some participants, and the device sleeve, although specific to that ICS, did not always fit the patient's canister. Additionally, when issues did arise, the time difference between our institution and the RTMM device company in Auckland, New Zealand, resulted in delays.

Technological challenges can be particularly problematic when working with a patient population that is known to struggle with having a stable home environment and are prone to losing things.⁸ Even with a working, compatible device, in 3 instances the study participant failed to refill their prescription, resulting in a lapse in medication monitoring. Additionally, if a participant lost an RTMM device (which occurred 4 times), the data could not be recovered. In addition to data loss, the study suffered a \$200 deficit with each device that was not returned. Finally, 5 participants allocated to receive the text messaging intervention struggled to maintain the same, working cell phone (ie, lost cell phone; no cell phone minutes; cell phone change) for the duration of the study, which intermittently prevented them from receiving the text messaging intervention.

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