1	
2	
3	Premonitory urge and tic severity, comorbidities, and quality of life in chronic
4	tic disorders
5	
6	Valerie Brandt, PhD ^{1,2} Jana Essing, MD ² Ewgeni Jakubovski, PhD ² Kirsten Müller-Vahl, MD ²
7	
8	¹ School of Psychology, Centre for Innovation in Mental health, University of Southampton,
9	Southampton, UK
10	² Clinic of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School,
11	Hanover, Germany
12	
13	
14	RUNNING TITLE: Urge characteristics in patients with tics
15	
16	Word Count: 3485
17	Abstract: 247
18	
19	Corresponding author: Valerie Brandt, University of Southampton, Building 44, University
20	Road, SO17 1BJ Southampton, UK, Phone: +44 23 8059 1375, E-Mail: v.c.brandt@soton.ac.uk
21	
22	Key words: Tourette syndrome, chronic tic disorder, premonitory urge (PU), quality of life,
23	comorbidity
24	
25	

26 Abstract

- Background: Tics are intimately associated with premonitory urges (PU) but knowledge about
 urges is still limited, with small sample sizes often limiting the generalizability of findings.
- 29 **Objectives:** This study addressed the following open questions: a) is tic severity associated with
- 30 urge severity, b) how common is relief, c) which comorbidities are associated with urges, d) are
- 31 urges, tics, and comorbidities associated with lower quality of life, and e) can complex and simple,
- 32 motor and vocal tics be differentiated based on PU?
- 33 Methods: N = 291 patients who reported a confirmed diagnosis of chronic primary tic disorder
- 34 (age=18-65, 24% female) filled out an online survey assessing demographic data, comorbid
- 35 conditions, location, quality and intensity of PU, as well as quality of life. Every tic was
- 36 recorded, and whether the patient experienced a PU, the frequency, intensity, and quality of that
- 37 urge.
- **Results:** PU and tic severity were significantly associated, and 85% of urge-related tics were
- 39 followed by relief. A diagnosis of attention deficit/hyperactivity disorder (ADHD) or depression,
- 40 female gender, and older age increased the likelihood of experiencing PU, while more obsessive
- 41 compulsive (OCD) symptoms and younger age were associated with higher urge intensities. PU,
- 42 complex vocal tics, ADHD, OCD, anxiety, and depression were related to lower quality of life.
- 43 Motor and vocal, complex and simple tics did not differ regarding PU intensity, frequency, and
- 44 quality, or relief.

45 **Conclusions:** The results shed light on the relationship between PU, tics, comorbidities, age,

46 gender, and quality of life in tic disorders.

48

49

50 Chronic primary tic disorders, including Tourette syndrome (TS), are characterized by multiple motor and/or vocal tics.¹ A preceding sensory or premonitory urge (PU) is considered a hallmark 51 52 of tics.²⁻⁴ The urge to tic has been compared to the urge to scratch - a build-up in tension or an 53 uncomfortable feeling that is relieved after an action. The estimate for the prevalence of PU varies, with approximately 77% of patients over 13 years and approximately 90% of patients over 18 54 years reporting to experience PU.^{2, 5-8} Adults with TS report urges more frequently than children 55 do, but it is unclear whether urges develop as a consequence of tics or precede tics in development; 56 alternatively, young children may simply lack awareness or the ability to describe PU.9 A recent 57 58 study of 291 patients confirmed that PU tend to occur in the same body part where a tic is about 59 to occur.¹⁰ The results indicated that, like tics¹¹, urges most commonly occur in the face and head.¹⁰ 60 Different qualities of urges (e.g. pressure) can be differentiated, for instance with the premonitory 61 urges for tics scale (PUTS).^{3, 12} There is evidence that the urge increases before a tic or a bout of 62 tics, and that the urge then decreases in the majority of patients^{13, 14} but a minority experiences the 63 reverse pattern.¹⁴ A recent study conducted in the same sample that is utilized in this study showed that 97% of patients who experienced urges also experienced relief for at least one of their tics.¹⁰ 64 However, it has not been investigated how many tics are associated with a sense of relief on 65 average, i.e. do patients experience a sense of relief with every tic or only for a subset of tics? 66 Patients with TS who seek diagnosis or treatment typically have at least one comorbidity, the most 67 68 common are attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), depression, and anxiety.¹⁵ Evidence on whether comorbidities are associated with urge 69 severity has been mixed,^{8, 12, 16-20} specifically, it is unclear whether or not comorbid OCD, ADHD, 70

71 depression, and anxiety are associated with the occurrence or intensity of PU. There is also some

vidence that different urge qualities may be related to comorbidities in different ways, e.g. OCD

may be associated with just-right feelings and ADHD may be related to feelings of tension.¹⁶ PU
have been found to be associated with lower quality of life^{8, 21} but it has not been investigated
whether different urge qualities are associated with lower quality of life.

While tics can be successfully treated with behavioral therapy,²²⁻²⁶ pharmacotherapy (most
 commonly anti-dopaminergic drugs,^{27,28} cannabis-based medicine including tetrahydrocannabinol

(THC),²⁹⁻³¹ and - in rare and otherwise treatment resistant cases – with surgical therapy using deep
 brain stimulation (DBS),³² it is less clear how different treatments may affect PU.³³

The current study aims to address whether urge severity and tic severity are associated, by using data from a survey that assessed each tic and associated PU individually. This detailed data allows us to investigate which urge qualities may be more common than others and how comorbidities are related to different urge qualities. Moreover, the sample is large enough to assess the impact of tics, urges, and comorbidities on quality of life, while controlling for age and gender. Finally, the association between anti-dopaminergic medication and urge occurrence (yes / no) and severity is investigated.

87

88 Methods

N = 291 patients (age = 18-65 years, 24% female) who reported a confirmed diagnosis of chronic primary tic disorder and who determined this diagnosis (e.g., Psychiatrist, neurologist) filled out an online survey. The data was mainly collected as part of a study that aimed to investigate how urges are distributed across the body.¹⁰ However, the dataset provides rich information on a number of unanswered questions in the field and thus serves for further analyses. For information on patient recruitment, survey procedure and demographic characteristics please see.¹⁰

95

96 Are urge and tic frequency and intensity associated?

97 Using the adult tic questionnaire (ATQ),³⁴ patients reported for each single tic they experienced (i) 98 how frequently they experienced the tic (1=sometimes, 2=multiple times a day, 3=once per hour, 99 4=all the time), (ii) how intense the tic was ('how intense was the tic in the last week?'1 [barely 100 noticeable] -4 [clearly noticeable by others, potentially painful]), (iii) how frequently they 101 experienced an urge (never, sometimes, always) with every tic, and (iv) how intense this urge was 102 (1 [very low intensity]-11 [very high intensity]). Pearson's correlations were conducted to explore 103 the association between these variables separately in motor and vocal tics, single and complex tics.

104

105 How common is a momentary sense of relief after a tic?

For each tic, patients reported whether they experienced a sense of relief (yes=1, no=0). Thepercentage of tics that were associated with a sense of relief was calculated.

109 Which urge qualities are most common?

110 Patients reported different PU qualities, reflecting the six PUTS urge quality categories¹² (feeling 111 itchy, pressure, tension, not just-right, incomplete, energy) and an additional two items that break down the last PUTS item into two separate questions (the feeling that something is building before 112 113 a tic, feeling discomfort) for different tics, i.e. a certain quality for each tic. Whether a patient 114 experienced a certain urge quality with at least one tic was coded as yes/no (1/0). Percentages of tics associated with different urge quality are reported overall and split by simple and complex as 115 116 well as motor and vocal tics. Chi-square tests were run between the different urge quality 117 categories on tics overall and corrected for multiple testing. Only p <.001 was considered 118 significant.

The number of patients who experienced different urge qualities were entered as the dependent variable in a repeated measures ANOVA. Contrasts were calculated between the different urge qualities. Mean urge intensity was calculated across tics within each patient per urge quality. Only nine patients reported experiencing every urge quality. Therefore, paired-t-tests were computed, comparing each urge quality to all others and these were corrected for multiple comparisons. Only p <.001 was considered significant.</p>

125

126 Are comorbidities associated with the urge to tic?

127 Comorbidities were assessed in two different ways. Patients filled out the Obsessive Compulsive Inventory-Revised (OCI-R)³⁵, a self-report scale with good reliability, convergent and divergent 128 validity.36,37 Current ADHD symptoms were assessed with the German ADHD self-rating scale 129 (ADHS-SB),³⁸ symptoms of depression were assessed with the Beck Depression Inventory (BDI-130 II),³⁹ and symptoms of anxiety were assessed using the Beck Anxiety Inventory (BAI).⁴⁰⁻⁴² Patients 131 132 were also asked to report any of the following comorbid diagnoses: ADHD (N=41; impulsivity, 133 hyperactivity, and inattention were also reported separately), OCD (N=157), anxiety disorders 134 (N=61), depression (N=73), sleeping disorders (N=40), eating disorders (N=14), personality 135 disorders (N=18) and addiction disorders (N=5). The diagnoses were entered into a binary logistic 136 regression (except addiction disorders and eating disorders, due to low prevalence) to predict the 137 likelihood of experiencing urges. Total number of comorbidities was correlated with urge intensity. 138

A structural equation model (SEM) was used to test the association of ADHD, OCD, anxiety, and
 depression, with the number of tics in each patient that were associated with a particular urge
 quality.

142

143 Symptom severity and quality of life

Linear regression was used to predict quality of life from urge qualities, comorbidities, and different types of tics, age and gender. Frequency of tics in different body areas were averaged according to the following body areas: eyes, nose/lips, grimacing, mouth/jaw, head, body, arms and legs as well as when classified as complex motor / vocal tics, e.g. copropraxia, echolalia.

148

149 Treatment

150 Independent t-tests were used to compare different current treatments (anti-dopaminergic 151 medication (N = 126) to no treatment (N=137). Behavioral therapy (N=11), and cannabis-based 152 treatment (N=16) were not analyzed due to low numbers.

- 153
- 154
- 155 *Results*

156 Is urge frequency and intensity associated with tic frequency and intensity?

157 A significant repeated measures ANOVA F(3,396)=9.90, p<.001, $\eta^2=.07$ showed that patients 158 executed complex motor tics F(1,132)=20.49, p<.001, $\eta^2=.13$, and complex vocal tics 159 F(1,132)=13.28, p<.001, $\eta^2=.09$ less frequently than simple motor tics, but not simple vocal tics 160 F(1,132)=1.13, p<.289, $\eta^2=.01$. In contrast, tic intensity did not differ significantly across simple

- 161 and complex motor and vocal tics $F(3,396)=2.42, p<.065, \eta^2=.02$.
- 162 On average, tic frequency was significantly associated with urge frequency (r=.27, p<.001), for
- both motor tics (r=.27, p<.001), and vocal tics (r=.30, p<.001). If the frequency of all urges and
- 164 tics were considered and used as a sum score, the correlation was much higher (r=.84, p<.001).
- 165 Considering all tics, more frequent motor tics (r=.82, p<.001), and more frequent vocal tics (r=.76,
- 166 p < .001) were significantly associated with more frequent urges. Similar effect sizes were found
- 167 for simple (r=.80, p<.001), and complex tics (r=.80, p<.001).

168 On average, urge intensity was associated with tic intensity (r=.37, p<.001), similar effect sizes 169 were found for motor (r=.39, p<.001), and vocal tics (r=.47, p<.001), and for simple (r=.40, 170 p<.001) and complex tics (r=.30, p<.001).

171

172 How common is a sense of relief?

173 Of those patients who reported PUs, 97% (N = 224/232) reported a feeling of relief for a least one 174 of their tics. In those patients who did report a sense of relief, 85% of tics were associated with 175 relief. Eighty-eight percent of simple motor tics, 90% of complex motor tics, 86% of simple 176 phonetic tics, and 81% of complex phonetic tics were associated with relief.

177

178 Which urge qualities are most common?

179 Different urge qualities were experienced with decreasing frequencies of patients in the following 180 order, in a significant linear fashion: feelings of tension, pressure and the feeling that something 181 was building up, a feeling of energy that needs to be released, a just-right feeling, feeling 182 discomfort, an itch or incompleteness (Figure 1A, Supplementary Table 1); F(1,290)=161.49, 183 p < .001, $\eta^2 = .28$. Tension was experienced by significantly more patients than all other urge qualities (contrast between tension and pressure: F(1,290)=34.77, p<.001, $\eta^2=.11$), and a feeling 184 185 of incompleteness was experienced by significantly fewer patients than all other urge qualities 186 (contrast between incompleteness and itch: F(1,290)=6.05, p=.015, $\eta^2=.02$). The pattern was the 187 same across simple and complex, as well as motor and vocal tics (Figure 1B).

188 Urge intensity did not differ across urge qualities F(1,8)=.02, p=.896, $\eta^2=.002$ (Figure 1C).

A similar pattern was reflected in urge quality associated with tics. Most tics were associated with feelings of tension, while fewest tics were associated with a feeling of incompleteness. Correcting for multiple testing, only those two occurred at significantly different rates (t(290)=10.37, p=.001, d = .61). Again, the pattern was reflected in simple and complex as well as in motor and vocal tics (Figure 1D, Supplementary Table 1).

194

195 Are Comorbidities associated with the urge to tic?

Having comorbid depression or anxiety, being older, and being female were associated with being more likely to experience urges (χ^2 =49.52, *p*<.001, Nagelkerkes *r*²=.25; Table 1). Having more comorbidities was not associated with more intense urges (*r*=.09, *p*=.183) but with a higher 199 likelihood to experience urges (r = .19, p = .001). Higher urge intensity was only predicted by more 200 OCD symptoms and younger age (Table 1).

The SEM showed that different comorbidities were related to experiencing more intense urges of different qualities, e.g., ADHD was related to higher intensities of tension and the feeling of something building up before a tic, OCD was related to not-just-right feelings, tension, and energy, depression was associated with pressure, tension, energy, and the feeling that urges build up, while anxiety was associated with tension, not-just-right feelings, incompleteness, energy, and the feeling of something building up before a tic (Figure 2, Table 2).

207

208 Symptom severity and quality of life

Lower Quality of life (QoL) was associated with higher urge intensity (r=.28, p<.001) and higher

tic frequency (r=.13, p=.045). Linear regression showed that more complex vocal tics, and having

- comorbid OCD, ADHD, anxiety or depression were associated with lower QoL (F(18,272)=59.17,
- **212** $p < .001, r^2 = .80;$ Table 3).
- Tics in different body parts were not related to differences in quality of life F(9,21)=.47, p=.876.

215 Treatment

Patients who were taking anti-dopaminergic medication were significantly less likely to experience an urge (N=126) than those who were not t(261)=-2.92, p=.004. There were no differences in urge intensity between patients who took anti-dopaminergic medication and those who did not receive treatment t(202)=-.52, p=.605.

220

221 Discussion

222 Is urge frequency and intensity associated with tic frequency and intensity?

The results show that simple tics were executed more frequently than complex tics but that tic intensity did not differ between simple and complex tics. The results confirm that urge and tic frequency and urge and tic intensity are correlated. This is an important result because previous findings were mixed regarding the association between urges and tics.^{3, 12, 14, 17, 18, 43, 44} It has been unclear whether the relationship between urges and tics was not as close as assumed or whether the instruments to measure urges and tics influenced the association found. The majority of studies have found small-medium correlations between urges and tics,^{3, 12, 17, 43, 44} while others found no relationship.¹⁸ Our data from a large sample of patients clarifies that urges and tics are indeed
closely linked.

232 The current study did not use questionnaires asking about general tic and urge frequencies across 233 all tics. Instead, patients reported each tic and reported how frequent the tic was and how frequently 234 the associated urge occurred. This also disentangles frequency and intensity, concepts that are convoluted when using overall questionnaire scores assessing urge or tic severity^{12, 45}. Regarding 235 236 frequency, the association between average urge frequency and tic frequency was small-medium 237 but when all tics per patient were considered, the relationship was high (explained variance was 238 70%). Effects were of similar size for motor and vocal tics, as well as for simple and complex tics. 239 The results confirm that there is a close association between tic and urge frequency, i.e. tics that 240 occur more frequently are also associated with frequent urges.

Regarding intensity, correlations showed a medium relationship between urge intensity and tic intensity on average. Again, this was true for motor and vocal as well as for simple and complex tics. The result suggests that more intense urges are followed by more intense tics. This leads back to the question whether an intense urge 'requires' an intense tic to lead to relief or whether intense tics become associated with an intense urge to match the tic.

246

247 How common is a sense of relief?

248 In patients who experienced urges, over 80% of tics were associated with a sense of relief. Previous 249 research showed that on average, urges increase before tics and decrease after a bout of tics.¹³ This 250 pattern was found only in two thirds of patients, albeit in a small sample.¹⁴ Previous papers have 251 focused on how many patients experience relief after executing a tic and have found that >80% of patients experience a sense of relief with at least one tic.^{17,21,46} These results show that in patients 252 253 who do experience relief > 80% of tics are associated with a sense of relief. Again, there were no 254 substantial differences between simple and complex or motor and vocal tics. Therefore, it remains 255 an open question what determines whether a tic is associated with a feeling of relief, and it poses 256 the question of whether it is sensible to categorize tics in this manner.

257

258 Which urge qualities are most common?

Regarding urge quality, tension was the most commonly experienced PU, while incompleteness
was the least common one. Again, there were no differences between vocal and motor tics, simple

and complex tics. Furthermore, different urge qualities were not associated with different 261 262 intensities. As far as we are aware, this is the first study to explore which urge qualities are most 263 commonly associated with tics. It is interesting that most tics were associated with general feelings of energy, tension, and discomfort, while more specific qualities such as an itch, feelings of 264 265 incompleteness and not just-right feelings were less common. This poses a problem regarding the assessment of PU with the PUTS.¹² The PUTS treats all qualities equally, and patients who score 266 267 higher on more different qualities, receive a higher urge severity score based on the questionnaire. 268 This would result in patients with high urge scores to have an unusual, rather than a usual 269 presentation of urges. Future versions should disentangle urge quality and intensity⁴⁷.

270

271 Are Comorbidities associated with the urge to tic?

272 When considering comorbid diagnoses, ADHD and depression were associated with a higher 273 likelihood to experience urges, while OCD was associated with higher urge intensities in those 274 that experienced urges. ADHD, OCD, and depression are common comorbidities in TS.¹⁵ Previous findings on the association between urges and comorbidities have been mixed.^{12, 17-19} No 275 276 relationship was found between PU severity and severity of ADHD and OCD in a sample of 122 277 adolescents and young adults,¹⁷ while a study in 42 youths found significant relationships between 278 PU and OCD, ADHD, and anxiety/depression.¹² Significant relationships between PU and OCD 279 symptoms and depression but not anxiety and ADHD were found in children older than 10 years,¹⁸ 280 and correlations of PU intensity with OCD but not ADHD were also found in 22 adults.¹⁶ The 281 results in this large sample of adults clarify that adult patients with ADHD and depression are more 282 likely to experience PU, and that patients who do experience PU, experience higher intensities 283 with more OCD symptoms, when age and gender effects are controlled for. Interestingly, having 284 more comorbidities was not associated with more intense urges but it was associated with a slightly 285 higher risk to experience urges in the first place.

Regarding urge quality, symptoms of ADHD were significantly associated with more intense feelings of tension. It might be assumed that inattention could lead to a reduced ability to perceived urges, therefore, the result is surprising. It is possible that the result reflects the difficulty to disentangle symptoms and experience of disorders that we currently regard as distinct, such as TS and ADHD. However, if ADHD patients experience an increased inner restlessness or tension overall, it may not be a distinct experience from the phenomena associated with tics. OCD was related to more intense feelings of tension, not just-right feeling, and energy. The results are in line with previous literature, showing that comorbid OCD was associated with not just-right feelings and feelings of incompleteness, and comorbid ADHD was associated with feelings of tension.¹⁶ In addition, our results showed that anxiety was related to more intense feelings of tension, not-just-right feelings, incompleteness, and energy. Depression was related to more intense feelings of pressure, tension, energy and a build-up of urges.

- 298 Further, older age and female gender were associated with a higher likelihood of experiencing urges in many^{2, 7, 8} but not all studies.¹⁷ This study shows that the likelihood of urges increases 299 300 across adulthood as well, not only across early development. In contrast, urge intensity decreased 301 with older age. The data suggest that if tics continue in a patient, the likelihood to experience urges 302 increases during adulthood. This would support the view that tics drive the generation of the urge 303 to tic over time, not the other way around. Regarding gender, there could be differences in attention to inner states⁴⁸ or the ability to identify inner states between males and females. However, very 304 305 little is known about gender differences and symptom development into older adult age in patients 306 with TS.
- 307

308 How are urges related to quality of life?

Lower quality of life was related to higher urge intensity and tic frequency. Higher symptom load for ADHD, OCD, depression, and anxiety, and more complex vocal tics were all significantly associated with lower quality of life. This is in line with the literature, showing that tic severity, urges,^{8,21} depression,⁴⁹ ADHD, and complex tics⁵⁰ are associated with lower quality of life. Specific urge qualities were not associated with lower quality of life once comorbidities were accounted for.

315

316 Treatment

Anti-dopaminergic medication was associated with a lower likelihood to experience urges but not lower urge intensity. Although no causal conclusions can be drawn due to the cross-sectional nature of the study, it seems unlikely that only patients with a lower likelihood to experience urges would choose medication as treatment. Anti-dopaminergic medication has a variety of effects, such as feeling sleepy or drowsy, that could affect the ability to perceive urges by decreasing interoceptive awareness.⁴⁸ It is also possible that anti-dopaminergic medication decreases the urge
to tic but possible mechanisms need to be further investigated.

324

325 Limitations

Patients who participated in this study reported that they were pre-diagnosed, however, they were not seen by a clinician for this study to confirm their diagnosis. This was also true for the comorbid diagnoses that were reported by participants. However, patients were recruited via TS outpatient groups and TS advocacy groups, and patients who reported that their diagnosis was not confirmed by a clinician were excluded from the analyses. Patients received €25 for their participation, and this poses a small risk of multiple participation but we would consider that risk small, due to the time it took to fill out the questionnaire.

333

334 Conclusions

335 Results from this large dataset clarify that urges and tics are closely associated, and that most tics 336 are followed by a feeling of relief. While the likelihood to experience urges appears to increase for 337 females, as well as across the adult lifespan, urge intensity decreases with age. Quality of life was 338 impacted by PU, comorbid ADHD, OCD, anxiety, and depression, as well as the number of 339 complex tics but not by motor tics or simple tics, confirming that as a rule, comorbid disorders and 340 PU are more detrimental to quality of life than tics are. Motor and vocal, complex and simple tics did not differ with regard to urge intensity, urge frequency, relief, and urge quality, posing the 341 342 question whether it is sensible to differentiate between these specific categories regarding tic disorder diagnosis. 343

344

345 Acknowledgment

346 We thank all patients for participation in this study. We thank the Else Kröner-Fresenius

347 foundation for supporting this project. The funders were not involved in the data collection,

analysis, or manuscript writing.

349

350 Ethical Compliance Statement

351 The Hanover Medical School ethics committee reviewed and approved the research (7631). The

research was conducted online, patients gave their informed consent to participate by ticking the

353 consent box on the SocSci Survey platform. We confirm that we have read the Journal's position 354 on issues involved in ethical publication and affirm that this work is consistent with those 355 guidelines. We confirm that we have read the Journal's position on issues involved in ethical 356 publication and affirm that this work is consistent with those guidelines.

- 357
- 358

359 Funding Sources and Conflict of Interest:

This work was partly supported by the Else Kröner-Fresenius-Stiftung within the KlinStrucMed programme 2017–2018 of the Hannover Biomedical Research School without being involved in the study design, the collection/analysis/in- terpretation of the data, the writing of the report, or the

363 publication process. No conflicts of interest to disclose.

364

365 Financial disclosures for the previous 12 months:

- 366 Valerie Brandt received funding from the Academy of Medical Sciences. She has received
- 367 royalties from Kohlhammer.
- 368
- 369 Kirsten Müller-Vahl has received financial or material research support from EU (FP7-

370 HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), DFG: GZ MU 1527/3-1 and

GZ MU 1527/3-2, BMBF: 01KG1421, National Institute of Mental Health (NIMH), Tourette

372 Gesellschaft Deutschland e.V., Else-Kröner-Fresenius-Stiftung, GW pharmaceuticals, Almirall

- 373 Hermal GmbH, Abide Therapeutics, and Therapix Biosiences.
- 374 She has received consultant's and other honoraria from Abide Therapeutics, adjupharm, Alexion,

375 AMP Alternative Medical Products GmbH, Ingelheim International GmbH, Bionorica Ethics

376 GmbH, CannaMedical Pharma GmbH, Canopy Grouth, Columbia Care, CTC Communications

- 377 Corp., Demecan, Enua pharma, Ethypharm GmbH, Eurox Group, Global Praxis Group Limited,
- 378 Lundbeck, MCI Germany, Neuraxpharm, Sanity Group, Stadapharm GmbH, Synendos
- 379 Therapeutics AG, Syqe, Tilray, and Zambon.
- 380 She is an advisory/scientific board member for Alexion, Branchenverband Cannabiswirtschaft
- e.V. (BvCW), CannaMedical Pharma GmbH, Bionorica Ethics GmbH, CannaXan GmbH,
- 382 Canopy Growth, Columbia Care, Ethypharm GmbH, IMC Germany, Leafly Deutschland GmbH,
- 383 Neuraxpharm, Sanity Group, Stadapharm GmbH, Synendos Therapeutics AG, Syqe Medical

384	Ltd., Therapix Biosciences Ltd., Tilray, von Mende Marketing GmbH, Wayland Group, and
385	Zambon.

- 386 She has received speaker's fees from Aphria Deutschland GmbH, Almirall, Bedrocan, Camurus,
- 387 CEREBRO SPAIN BIDCO S.L, Cogitando GmbH, Emalex, Eurox Deutschland GmbH, Ever
- 388 pharma GmbH, GROW, Hessische Landesstelle für Suchtfragen e.V. (HLS), LIO
- 389 Pharmaceuticals GmbH, Medizinischer Dienst Westfalen Lippe, Meinhardt Congress GmbH, PR
- Berater, Spectrum Therapeutics GmbH, Takeda GmbH, Tilray, and Wayland Group.
- 391 She has received royalties from Deutsches Ärzteblatt, Der Neurologie und Psychiater, Elsevier,
- 392 Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, and Kohlhammer.
- 393 She served as a guest editor for Frontiers in Neurology on the research topic "The neurobiology
- and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative
- 395 projects", is an associate editor for "Cannabis and Cannabinoid Research" and an Editorial Board
- 396 Member of "Medical Cannabis and Cannabinoids" und "MDPI-Reports" and a Scientific board
- 397 member for "Zeitschrift für Allgemeinmedizin".
- 398

399 Authors' Roles

- 400 1) Research project: A. Conception, B. Organization, C. Execution
- 401 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique
- 402 3) Manuscript: A. Writing of the first draft, B. Review and Critique
- 403
- 404 Valerie Brandt: 1A, 2A, 2B, 31
- 405 Jana Essing: 1A, 1B, 1C, 2C, 3B
- 406 Ewgeni Jakubovski: 1A, 1B, 2C, 3B
- 407 Kirsten R Müller-Vahl: 1A, 1B, 2C, 3B
- 408
- 409
- 410

411 References

412 1. DSM-5. Diagnostic and statistical manual of mental disorders. 5 ed. Arlington, VA:
413 American Psychiatric Publishing, 2013.

414 2. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J
415 Psychiatry 1993;150(1):98-102.

416 3. Crossley E, Seri S, Stern JS, Robertson MM, Cavanna AE. Premonitory urges for tics in adult
417 patients with Tourette syndrome. Brain Dev 2014;36(1):45-50.

- 418 4. Capriotti MR, Brandt BC, Turkel JE, Lee HJ, Woods DW. Negative Reinforcement and
 419 Premonitory Urges in Youth With Tourette Syndrome: An Experimental Evaluation. Behav Modif
 420 2014;38(2):276-296.
- 421 5. Bliss J. Sensory experiences of Gilles de la Tourette syndrome. Arch Gen Psychiatry 422 1980;37(12):1343-1347.

423 6. Kwak C, Dat Vuong K, Jankovic J. Premonitory sensory phenomenon in Tourette's 424 syndrome. Mov Disord 2003;18(12):1530-1533.

425 7. Sambrani T, Jakubovski E, Muller-Vahl KR. New Insights into Clinical Characteristics of
426 Gilles de la Tourette Syndrome: Findings in 1032 Patients from a Single German Center. Front
427 Neurosci 2016;10:415.

428 8. Crossley E, Cavanna AE. Sensory phenomena: clinical correlates and impact on quality of 429 life in adult patients with Tourette syndrome. Psychiatry Res 2013;209(3):705-710.

430 9. Banaschewski T, Woerner W, Rothenberger A. Premonitory sensory phenomena and
431 suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents.
432 Dev Med Child Neurol 2003;45(10):700-703.

433 10. Essing J, Jakubovski E, Psathakis N, Cevirme SN, Leckman JF, Muller-Vahl KR. Premonitory
434 Urges Reconsidered: Urge Location Corresponds to Tic Location in Patients With Primary Tic
435 Disorders. J Mov Disord 2022;15(1):43-52.

436 11. Jankovic J. Tourette syndrome. Phenomenology and classification of tics. Neurol Clin437 1997;15(2):267-275.

438 12. Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial
439 psychometric results and examination of the premonitory urge phenomenon in youths with Tic
440 disorders. J Dev Behav Pediatr 2005;26(6):397-403.

441 13. Brandt VC, Beck C, Sajin V, et al. Temporal relationship between premonitory urges and
442 tics in Gilles de la Tourette syndrome. Cortex 2016;77:24-37.

443 14. Schubert L, Verrel J, Behm A, Baumer T, Beste C, Munchau A. Inter-individual differences
444 in urge-tic associations in Tourette syndrome. Cortex 2021;143:80-91.

- Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic
 relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry
 2015;72(4):325-333.
- 448 16. Brandt VC, Beck C, Sajin V, Anders S, Munchau A. Convergent Validity of the PUTS.
 449 Frontiers in Psychiatry 2016;7:51.
- 450 17. Reese HE, Scahill L, Peterson AL, et al. The premonitory urge to tic: measurement, 451 characteristics, and correlates in older adolescents and adults. Behav Ther 2014;45(2):177-186.

452 18. Steinberg T, Shmuel Baruch S, Harush A, et al. Tic disorders and the premonitory urge. J

453 Neural Transm (Vienna) 2010;117(2):277-284.

454 19. Rajagopal S, Cavanna AE. Premonitory urges and repetitive behaviours in adult patients 455 with Tourette syndrome. Neurol Sci 2014;35(6):969-971.

456 20. Eddy CM, Cavanna AE. Premonitory Urges in Adults With Complicated and Uncomplicated
457 Tourette Syndrome. Behav Modif 2014;38(2):264-275.

458 21. Cavanna AE, David K, Orth M, Robertson MM. Predictors during childhood of future
459 health-related quality of life in adults with Gilles de la Tourette syndrome. Eur J Paediatr Neurol
460 2012;16(6):605-612.

- Wilhelm S, Deckersbach T, Coffey BJ, Bohne A, Peterson AL, Baer L. Habit reversal versus
 supportive psychotherapy for Tourette's disorder: a randomized controlled trial. Am J Psychiatry
 2003;160(6):1175-1177.
- 464 23. Dutta N, Cavanna AE. The effectiveness of habit reversal therapy in the treatment of 465 Tourette syndrome and other chronic tic disorders: a systematic review. Funct Neurol 466 2013;28(1):7-12.
- 467 24. Schaich A, Brandt V, Senft A, et al. Treatment of Tourette Syndrome With Attention
 468 Training Technique-A Case Series. Front Psychiatry 2020;11:519931.
- Verdellen CW, Keijsers GP, Cath DC, Hoogduin CA. Exposure with response prevention
 versus habit reversal in Tourettes's syndrome: a controlled study. Behav Res Ther
 2004;42(5):501-511.
- 472 26. Andren P, Jakubovski E, Murphy TL, et al. European clinical guidelines for Tourette
 473 syndrome and other tic disorders-version 2.0. Part II: psychological interventions. Eur Child
 474 Adolesc Psychiatry 2022;31(3):403-423.
- 475 27. Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette
 476 syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc
 477 Psychiatry 2011;20(4):173-196.
- 478 28. Roessner V, Eichele H, Stern JS, et al. European clinical guidelines for Tourette syndrome
 479 and other tic disorders-version 2.0. Part III: pharmacological treatment. Eur Child Adolesc
 480 Psychiatry 2022;31(3):425-441.
- 481 29. Muller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of
 482 Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on
 483 neuropsychological performance. Neuropsychopharmacology 2003;28(2):384-388.
- 484 30. Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with 485 Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry 486 2002;35(2):57-61.
- 487 31. Muller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is 488 effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin 489 Psychiatry 2003;64(4):459-465.
- 32. Szejko N, Worbe Y, Hartmann A, et al. European clinical guidelines for Tourette syndrome
 and other tic disorders-version 2.0. Part IV: deep brain stimulation. Eur Child Adolesc Psychiatry
 2022;31(3):443-461.
- 493 33. Verdellen CW, Hoogduin CA, Kato BS, Keijsers GP, Cath DC, Hoijtink HB. Habituation of
 494 premonitory sensations during exposure and response prevention treatment in Tourette's
 495 syndrome. Behav Modif 2008;32(2):215-227.

496 34. Abramovitch A, Reese H, Woods DW, et al. Psychometric Properties of a Self-Report 497 Instrument for the Assessment of Tic Severity in Adults With Tic Disorders. Behav Ther 498 2015;46(6):786-796.

499 35. Foa EB, Huppert JD, Leiberg S, et al. The Obsessive-Compulsive Inventory: development
500 and validation of a short version. Psychol Assess 2002;14(4):485-496.

501 36. Gonner S, Leonhart R, Ecker W. The Obsessive-Compulsive Inventory-Revised (OCI-R): 502 validation of the German version in a sample of patients with OCD, anxiety disorders, and 503 depressive disorders. J Anxiety Disord 2008;22(4):734-749.

50437.Hajcak G, Huppert JD, Simons RF, Foa EB. Psychometric properties of the OCI-R in a college505sample. Behav Res Ther 2004;42(1):115-123.

506 38. Rosler M, Retz W, Retz-Junginger P, et al. [Tools for the diagnosis of attention-507 deficit/hyperactivity disorder in adults. Self-rating behaviour questionnaire and diagnostic 508 checklist]. Nervenarzt 2004;75(9):888-895.

50939.Kuhner C, Burger C, Keller F, Hautzinger M. [Reliability and validity of the Revised Beck510Depression Inventory (BDI-II). Results from German samples]. Nervenarzt 2007;78(6):651-656.

511 40. Steer RA, Rissmiller DJ, Ranieri WF, Beck AT. Structure of the computer-assisted Beck 512 Anxiety Inventory with psychiatric inpatients. J Pers Assess 1993;60(3):532-542.

513 41. Kabacoff RI, Segal DL, Hersen M, Van Hasselt VB. Psychometric properties and diagnostic 514 utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult 515 psychiatric outpatients. J Anxiety Disord 1997;11(1):33-47.

42. de Beurs E, Wilson KA, Chambless DL, Goldstein AJ, Feske U. Convergent and divergent
validity of the Beck Anxiety Inventory for patients with panic disorder and agoraphobia. Depress
Anxiety 1997;6(4):140-146.

519 43. Baumung L, Muller-Vahl K, Dyke K, et al. Developing the Premonitory Urges for Tic 520 Disorders Scale-Revised (PUTS-R). J Neuropsychol 2020:e12216.

44. Raines JM, Edwards KR, Sherman MF, et al. Premonitory Urge for Tics Scale (PUTS):
replication and extension of psychometric properties in youth with chronic tic disorders (CTDs).
J Neural Transm (Vienna) 2017.

Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing
of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28(4):566-573.

526 46. Ganos C, Kahl U, Schunke O, et al. Are premonitory urges a prerequisite of tic inhibition 527 in Gilles de la Tourette syndrome? J Neurol Neurosurg Psychiatry 2012;83(10):975-978.

528 47. Baumung L, Muller-Vahl K, Dyke K, et al. Developing the Premonitory Urges for Tic 529 Disorders Scale-Revised (PUTS-R). J Neuropsychol 2021;15(1):129-142.

530 48. Ganos C, Garrido A, Navalpotro-Gomez I, et al. Premonitory urge to tic in Tourette's is 531 associated with interoceptive awareness. Mov Disord 2015;30(9):1198-1202.

532 49. Jalenques I, Galland F, Malet L, et al. Quality of life in adults with Gilles de la Tourette533 Syndrome. BMC Psychiatry 2012;12:109.

534 50. Eapen V, Snedden C, Crncec R, Pick A, Sachdev P. Tourette syndrome, co-morbidities and 535 quality of life. Aust N Z J Psychiatry 2016;50(1):82-93.

536

538	Figure Legends
539	Figure 1A: Number of patients (±Standard Error) experiencing urge quality associated with at
540	least one tic.
541	B: Percentage of patients reporting each urge quality for at least one tic (multiple responses
542	possible).
543	C: average urge intensity associated with tics.
544	D: Percentage of tics associated with different types of urge quality.
545	
546	
547	Figure 2. Structural equation model. Significant beta values are displayed in the model.
548	Correlations amongst the predictors are also displayed. ADHD = attention deficit hyperactivity
549	disorder OCD = obsessive compulsive disorder.
550	
551	
552	

553 Supplementary Table Legend:

- 555 Supplementary Table 1. Quality of urges: N of patients. The first row shows urge quality per
- 556 patient for at least one tic. Second row: number of tics associated with different urge qualities.
- 557 SD=standard deviation. Lower part: total number and percentages of tics associated with
- 558 different urge qualities.
- 559
- 560

	Table 1. Regression predicting arges from comorbidities						
	В	S.E.	Wald	OR	р		
Constant	-2.83	1.15	6.04	.06	.014		
OCD	63	.34	3.38	1.88	.066		
Anxiety	.21	.51	.17	.81	.683		
Depression	2.07	.78	7.03	.13	.008		
ADHD	2.66	1.05	6.49	.07	.011		
Sleep	.37	.83	.20	.69	.653		
Personality	25	.90	.08	1.28	.783		
Age	.55	.19	8.37	1.73	.004		
Gender	2.76	1.04	7.10	15.83	.008		
	В	S.E.		Beta	р		
Constant	5.66	.43			.000		
ADHD	.02	.03		.04	.613		
OCD	.03	.01		.22	.017		
Anxiety	.01	.01		.06	.550		
Depression	.00	.01		02	.774		
Age	24	.10		16	.017		
Gender	.38	.26		.10	.150		

Table 1. Regression predicting urges from comorbidities

563 The upper panel shows a binary logistic regression with diagnosis (yes / no) as predictor

variables and experiencing urges (yes / no) as the dependent variable. Having a depression or

ADHD diagnosis significantly increased the likelihood to experience urges. Significant resultsare marked in bold.

The lower panel shows the results of a linear regression, predicting urge intensity fromquestionnaire data. Attention deficit hyperactivity disorder (ADHD) and younger age were

associated with more intense urges. OCD = obsessive compulsive disorder.

		Estimate	S.E.	Z	р
Itch					
	ADHD-SB	.07	.04	1.66	.097
	OCI-R	.03	.02	1.75	.080
	BAI	03	.02	-1.18	.239
	BDI-II	.03	.02	1.25	.211
Pressure					
	ADHD-SB	.09	.05	1.76	.078
	OCI-R	.03	.02	1.44	.151
	BAI	.04	.03	1.57	.118
	BDI-II	.06	.03	2.22	.027
Tension					
	ADHD-SB	.11	.04	2.64	.008
	OCI-R	.05	.02	2.79	.005
	BAI	.05	.02	2.03	.042
	BDI-II	.05	.02	2.12	.034
Just right					
-	ADHD-SB	.07	.04	1.72	.086
	OCI-R	.04	.02	2.47	.014
	BAI	.08	.02	4.05	<.001
	BDI-II	.01	.02	.56	.573
Incompleteness					
	ADHD-SB	.00	.04	.10	.918
	OCI	.02	.02	1.12	.263
	BAI	.05	.02	2.60	.009
	BDI-II	.01	.02	.29	.771
Energy					
	ADHD-SB	.03	.05	.49	.627
	OCI-R	.06	.02	2.67	.008
	BAI	09	.03	-3.14	.002
	BDI-II	.08	.03	2.79	.005
Discomfort					
	ADHD-SB	.08	.05	1.76	.079
	OCI-R	.00	.02	.10	.924
	BAI	07	.02	-2.89	.004
	BDI-II	.10	.03	3.98	<.001
Build-up					
	ADHD-SB	.12	.05	2.70	.007
	OCI-R	.02	.02	.75	.455
	BAI	06	.02	-2.67	.008
	BDI-II	.07	.02	2.77	.006

Table 2. Association between different urge qualities and comorbidities

581 The table shows which comorbidities are associated with different urge qualities. Significant

associations are highlighted in bold. ADHD-SB = attention deficit hyperactivity disorder self-

rating scale, OCI-R = obsessive compulsive inventory, BDI-II = Beck Depression Inventory II,

584 BAI=Beck Anxiety Inventory.

Table 5. Variables that predict quality of the							
	В	S.E.	ß	t	р		
(Constant)	1.08	2.24		.48	.632		
N Simple Motor Tics	.10	.21	.02	.49	.625		
N Complex Motor Tics	.50	.29	.09	1.69	.091		
N Simple Vocal Tics	12	.31	02	39	.699		
N Complex Vocal Tics	1.85	.55	.14	3.34	.001		
ADHD-SB	1.10	.15	.29	7.51	<.001		
OCI-R	.17	.06	.11	2.60	.010		
BAI	.36	.08	.23	4.52	<.001		
BDI-II	.63	.08	.32	8.10	<.001		
Itch	.47	1.38	.01	.34	.734		
Pressure	.66	1.47	.02	.45	.652		
Tension	58	1.62	01	36	.720		
Just right	.20	1.58	.00	.12	.901		
Incomplete	-3.00	1.63	06	-1.85	.066		
Energy	47	1.32	01	35	.725		
Discomfort	.35	1.85	.01	.19	.852		
Build-up	-1.11	1.99	03	56	.576		
Age	39	.52	02	76	.450		
Gender	67	1.44	01	47	.641		

Table 3. Variables that predict quality of life

587

588 A linear regression showed that a higher number of complex vocal tics, and higher symptoms of

attention deficit hyperactivity disorder (ADHD-SB), obsessive compulsive disorder (OCD-R),

590 anxiety, and depression were associated with lower quality of life. BDI-II = Beck Depression

591 Inventory II, BAI=Beck Anxiety Inventory.

592