HHS Public Access
Author manuscript
J Dev Behav Pediatr. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:
J Dev Behav Pediatr. 2019 December ; 40(9): 751–761. doi:10.1097/DBP.0000000000000735.

Toilet Training in Fragile X Syndrome

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Abstract

Objective—To characterize bladder and bowel toileting skill acquisition in children with Fragile X syndrome (FXS) and to identify associated demographic, behavioral and clinical factors.

Method—Using baseline data from the Fragile X Online Registry with Accessible Research Database (FORWARD), bivariate analyses and logistic regression models were used to identify differences between subjects who were and were not bowel and/or bladder trained by age 10 years. Cox proportional hazards models were used to assess the rate of completion of toilet training as a function of sex and autism spectrum disorder (ASD) diagnosis.

Results—In bivariate analyses, male sex, lower language level, inability to write one's name, more impaired intellectual level, ASD, and more severe behavioral deficits all predicted lack of bladder training (n=313, $p<0.001$) and bowel training (n=300, p=0.0004 to 0.0001) by age 10. In logistic regression models, lower level of language acquisition ($p<0.001$) and higher Aberrant

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Disclosure Statement: None of the authors have any conflicts of interest relevant to this manuscript.

Behavior Checklist Irritability scores (p<0.04) were associated with lower odds of bladder training by age 10. Lower level of language acquisition (p<0. 001) and ASD (p<0.025) were associated with lower odds of bowel training by age 10. For both bladder and bowel training, Cox proportional hazard models indicated that delayed training was associated with male gender, lower levels of language acquisition and ASD for both bladder training (n=486; p<.001) and bowel training (n=472; p<.001).

Conclusion—These findings emphasize the importance of both slower language development and ASD diagnosis in predicting bowel and bladder training delays, and can be used to develop and evaluate targeted approaches to toilet training based on sex, ASD diagnosis, and other clinical features identified in this study.

Keywords

toilet training; Fragile X syndrome; Autism spectrum disorder

INTRODUCTION

Mastery of toileting has long been considered a critical life skill. Appropriate toileting behaviors can positively impact self-confidence, physical comfort, independence, social acceptance, and caregiver burden.[1,2] In typically developing children, toilet training (TT) begins at 18 to 24 months and ends by 24 to 36 months[3,4,5] of age in the United States. However, in children with intellectual and developmental disabilities (IDD), such as autism spectrum disorder (ASD), Fragile X syndrome (FXS), or Down syndrome (DS), TT onset and duration can be delayed significantly.[6] Due to a range of developmental impairments in areas such as cognition, speech and language, fine motor skills, social skills, and adaptive behaviors, there are varying degrees of functional limitations including toileting mastery.[6, 7] In fact, TT for children with IDD is one of the most frequently searched self-help areas.[8] In response to the need for guidance for families, researchers have proposed a variety of TT strategies for children with IDD, including hydration, frequent and/or scheduled opportunities for practice, scheduled sitting, video modeling and instruction, priming, graduated guidance, enuresis alarms, medication, positive reinforcement, punishment, and overcorrection.[1,8–11] While these strategies in combination have been successful, the majority of these practices have been developed for and implemented in children with ASD or unspecified intellectual disabilities (ID).

Specific toileting interventions designed for individuals with IDD include procedures that are generic in nature and frequently lack information to guide practices for diagnostically defined subgroups. While some guidelines may be helpful due to the utilization of basic behavioral approaches, extended maturation periods and environmental manipulations, there is a significant lack of information on the effectiveness of said guidelines for specific conditions. A comprehensive review conducted by Kroeger and Sorensen-Burnworth found the majority of the studies in this area focused on approaches based on the seminal work by Foxx and Azrin involving behaviorally based rapid toilet training (RTT).[11,12] This is not an ecological approach nor do the components applied in various studies take into account developmental or phenotypic strengths and weakness. There is also a paucity of information on the actual age of onset for successful TT and the developmental and physical factors present in those individuals for whom independent TT has not been achievable. This lack of information serves as a barrier to families and clinicians, as they are creating and implementing programs without crucial information on when it might be best to initiate a program and for whom a particular approach is most likely to prove effective. Such information could help inform families and clinicians in creating targeted plans for individuals with specific profiles thus decreasing frustration and unnecessary stress and increasing options for those for whom previous approaches have proven unsuccessful.

FXS, the most common form of inherited IDD, is a genetic disorder caused by a mutation on the X chromosome in the *fragile X mental retardation 1 gene* (*FMR1*).[13] It includes increased risk for a host of behavioral characteristics (e.g., anxiety, self-injurious behavior, poor eye contact, sensory processing disorder, repetitive/ritualized behavior and increased risk for aggression), executive functioning deficits (e.g., attention, working memory), and comorbid neurodevelopmental disorders such as ASD.[14,15] These behavioral characteristics in combination with cognitive and motor impairments can make acquisition of self-help skills challenging.[13] Furthermore, these impairments are such that the manner in which service providers and caregivers intervene is important. Considering both the prevalence of the disorder and the fact that parents are typically very interested in learning about the real-world implications of the disability (e.g., independent toileting, communication), the lack of previous research regarding the acquisition of toileting skills in the FXS population represents a significant gap in knowledge about a key problem associated with the disorder.[16] Moreover, it is clear from attendance at toilet training sessions at fragile X conferences, frequent TT concerns raised in clinical visits, and frequent listing of this as a limiting problem at family discussions, that TT issues are a significant issue for many families with children and adults with FXS. What little is known suggests that the majority of children with FXS learn to use the toilet between the ages of 6 to 10 and demonstrate independent toileting by adulthood (age 20+); wiping independently, however, remains an area for improvement in males.[16] In order to guide expectations, reduce discouragement and TT failures, and develop future FXS-specific TT protocols, there is a need in the literature for a more detailed profile of toileting in children with FXS and indeed, in conditions with IDD in general.

There is minimal prior literature on the topic of the timing of TT achievement in cohorts with IDD, and no studies that have established the most important predictors of delayed training. In a study of children with Down syndrome, parents reported that the average age of bladder training completion was 5.5 years compared to a control group report of 2.2 years.[4] Only 79% of children with Down syndrome were bladder trained by the age of 5 years. In a study of children with ID alone, the authors observed that 83% of mildly and 62% of profoundly affected children achieving dryness (urine) at seven years, with the age at bowel control ranging from 3 years in mildly affected to 10 years in profoundly affected children.[17] In a study of children with ASD and a separate group with ID, the authors reported that, the ASD group did more poorly than the ID group in toilet training, and that older children in both groups did better than younger children.[18] In another study of children with ASD alone, there was a trend for toileting being achieved at a higher age for those with more severe/profound ID (5.6 years for bladder and 7.1 years for bowel accomplishment) and for those with nonverbal status (5.3 years for bladder and 6.4 years for bowel accomplishment).[19] Yet another study explored TT in individuals with Angelman syndrome using a modified RR (response restriction) approach resulting in increased bladder control in individuals aged 6–25, however only three of the individuals maintained positive results after 3–18 months.[20] In the only study of individuals with FXS, toileting achievement, with no distinction made between bladder and bowel training, results were presented in age blocks and by sex; roughly 70% of males and 85% of females used the toilet independently from 6–10 years of age, with 100% of females at 11 years and older using the toilet independently, and 80–90% of males achieving accomplishment at later ages.[16]

The purpose of this study was to develop a better understanding of the acquisition of bladder and bowel toileting skills in children with FXS and to analyze factors associated with differences in TT such as sex, language skills, comorbid ASD, functional skills, and severity of behavioral problems. This study examines these factors together in order to tease out the most important predictors of lack of success with TT so that one can identify what practices might work better for individuals with these different characteristics.

METHODS

Data analyzed for this report were derived from Fragile X Online Registry with Accessible Research Database (FORWARD). As described in Sherman et al.[21], FORWARD is a multisite observational study initiated in 2012.[22] The analyses for this report were run using baseline data from FORWARD Version 3, with data obtained from 633 individuals with FXS evaluated between 2012 and 2016, who were at least one year of age at the time of evaluation, and who had data on bladder and/or bowel training. The study was approved by the Institutional Review Board for each participating FXS Clinic where data was collected, and written informed consent was obtained from primary caregivers or adult patients who were their own guardians.

Demographic variables including age, sex and ethnicity were collected on the Registry form. Data collected from the Parent Report form included responses to questions about the age of toilet training for bowel and bladder, or a response that the patient was not yet trained at the time of the visit. The question asked was “When was the child bladder (bowel) trained? (years and months)?” The intent of the toileting questions was that “trained” meant predominantly using the toilet for urination or bowel movements. Data from the Clinician Report form included variables that might be related to problems with TT including: presence of seizures, loose stools, constipation, seasonal allergies, use of medications (antiepileptics, stimulants, alpha-agonists, selective serotonin reuptake inhibitors (SSRIs), antipsychotics, or mood stabilizers), highest language milestone achieved, ability to write name, level of intellectual disability, and clinical diagnosis of ASD by DSM-IV-R/5 criteria.[22–25] Data from parent/caregiver-report standardized behavioral questionnaires included the Social Responsiveness Scale, Second Edition (SRS-2)[26] total score, Social Communication Questionnaire (SCQ)[27] total score, and Aberrant Behavior Checklist–Community (ABC)[28] Irritability and Hyperactivity domain total scores, based on ABC scoring according to the FXS-factored scoring algorithm (ABC^{FX})[29]. A variable based on new cut points on both the SCQ and SRS-2 following review for discriminating items and those with face validity (DFV criteria) was created to determine diagnosis for ASD using screening instruments versus clinical diagnosis.[30] The new cut points using Youden's J criteria following receiver operating characteristic curves were: SCQ ≥ 8 and SRS-2 ≥ 65 versus SCQ < 8 and SRS-2 < 65.

For bivariate and logistic regression analysis, the subgroup of patients that had reached the age of 10 years (n=313, 47.2% of the total sample) was divided into two groups: those who had toilet trained before age 10 and those not trained before 10 years of age. Each variable was compared for the percentage of patients who had trained by age 10 and those who had not, separately for each sex. The 10 year age cutoff was based on previous findings that indicate that by 11 to 15 years 80% of males and 100% of females were reportedly able to use the toilet independently with the greatest amount of growth in overall skill acquisition occurring in age groups birth to 5 and 6 to 10.[16] Males presented with steady increases in reported skill acquisition related to toileting through the age of 20; for females, there was no significant increase in toileting skills beyond the 6- to 10-year age group. As such the 10 years of age cutoff allowed for cross gender comparisons and reflected a natural growth curve break based on previous reports.[16]

DATA ANALYSIS

Frequency tabulations and proportions for categorical variables, and means and standard deviations, for continuous variables, were used for the descriptive analyses. The chi-square test for differences in proportions, the Wilcoxon Rank-Sum Test, and the Student t-test for differences between means were used to examine differences between subjects that were toilet trained (bladder or bowel) by 10 years of age versus those that were not toilet trained by 10 years of age, separately by gender. Multivariate logistic regressions were used to determine independent predictors of completed toilet training by 10 years of age, with predictors selected based on results from bivariate models, again separately by gender. Cox proportional hazards (PH) models were used to produce hazard ratios for completion of toilet training (the event), across the observation period (age) by sex and ASD status, using data from all participants older than 1 year of age with valid toilet training and predictor data, N=610). Separate multivariate PH models were also fit for each gender with selected predictors, in order to assess independent associations. Due to missing values for some of the predictors, fewer participants were included in these analyses (N=486). Using the same sample, Kaplan-Meier survival curves were used to graphically illustrate the time to toilet training as a function of sex. Analyses were performed using the Statistical Analysis Systems version 9.4 (SAS Inc., Cary, NC). The advantage of the Cox and Kaplan-Meier analyses is that toileting information obtained from children evaluated at ages younger than 10 could be included in the analysis, with censoring if the endpoint (toileting) had not been reached at the time of evaluation. In each analysis reported in this paper, data were used for all individuals who had valid values for the variables used in that analysis.

RESULTS

Characteristics of the 633 FORWARD participants with available toileting data used for this study are shown in Table 1: 77% were male 12% were of Spanish/Hispanic origin, 77% were White, 12% were African American/Black, and 4% were Asian; the median age at evaluation was 10.42 years. A history of seizures was reported for 12% of the sample, approximately 42% were diagnosed with ASD by a clinician, approximately half had moderate (43%) or severe (6%) intellectual disability and 91% showed indicators of hyperarousal. In order to identify clinical characteristics related to substantial delays in toilet training bivariate analyses were conducted comparing frequency of characteristics in patients who toilet trained before and after age 10 years, for both bladder and bowel training. For participants whose baseline evaluation was at age 10 or later and who had valid bladder training data (N=313), predictors of lack of bladder training by age 10 ($p<.001$), as shown in Table 2, were: male sex, lower language level, inability to write name, impaired intellectual level, presence of ASD by clinician report, ASD by DFV criteria SRS-2/SCQ cut points, and more severe behavior based on higher ABC^{FX} Irritability or Hyperactivity subscale scores). Use of alpha-agonists or antipsychotics for behavior were associated with lack of bladder training at $p<0.01$. History of seizures at any time, and presence of loose stools, constipation, seasonal allergies, food allergies, allergies to medications, as well as use of stimulants, SSRIs, non-SSRI antidepressants, mood stabilizers, anxiolytics, and other psychopharmacological medications for behavior at the time of the baseline visit were not significantly related to achievement of bladder training by age 10 ($p>.05$, data not shown).

Predictors of lack of bowel training in bivariate analysis ($p<.005$) were male sex, lower language level achieved, inability to write name, more impaired intellectual level, presence of ASD by clinician report ASD by DFV criteria SRS-2/SCQ cut points, presence of hyperarousal, use of alpha-agonists, use of antipsychotics, and more severe behavior based on higher ABC^{FX} Irritability or Hyperactivity subscale scores (Table 2). History of seizures was also greater among those who were not bowel trained by age 10 ($p=.04$). Presence of loose stools, constipation, or seasonal allergies as well as use of stimulants or SSRIs for behavior at the baseline visit were not significantly related to achievement of bowel training by age 10 (data not shown). Note that for both bowel and bladder training, median age at baseline evaluation was significantly greater for those who were reported to have been trained by age 10.

Because many of the predictors of very delayed TT identified in the bivariate analysis would potentially overlap in the same patients (e.g., more severe language functioning, more cognitive impairment, ASD diagnosis), we sought to determine which characteristic(s) were the most important drivers of TT delay, independent of the other characteristics. In order to determine the best independent predictors for toilet training by age 10, we used a multivariate logistic regression model that included the following predictor variables: sex, presence of seizures, intellectual disability level, language milestones achieved, presence of ASD diagnosis, and ABC Irritability score. The results are shown in Table 3: higher odds of bladder training were predicted by higher level of language acquisition ($p<0.001$), and a lower ABC Irritability score ($p=0.01$). Higher level of language acquisition ($p<0.001$), having no ASD diagnosis ($p=0.05$), and lower ABC Irritability score ($p=0.04$) were also associated with higher odds of bowel training by age 10. Sex, presence of seizures and intellectual level did not independently predict toilet training for either bowel or bladder after adjusting for the effects of the other variables.

In order to determine the amount of risk for lack of TT at a given age conveyed by the predictors identified in the bivariate analysis, multivariate Cox proportional hazard (risk) models were utilized. In these models, using data on bladder and bowel training data from participants evaluated at one year of age or greater, there were consistently strong effects of language acquisition and ASD status, on both bladder and bowel milestones achievements (Table 4). For each higher level of language milestone achieved, the likelihood of bladder and bowel training at any given age was approximately 2 times ($p<0.001$) that of each lower level for both males and females. Males without ASD were roughly 1.5 times as likely to achieve bladder and bowel training at any given age than those with ASD ($p<0.003$); and, for females without ASD there was almost a 2-fold increase in likelihood of achieving bowel training at any given age than females with ASD ($p<0.03$). For each reduction in the level of ID (milder level of impairment), there was a 1.5 fold increase ($p<0.003$) in the likelihood of bladder training for females only. For each decrement in ABC irritability score, there were only modest associations with bladder and bowel training.

Kaplan-Meier survival curves show the time to toilet training separated by sex and ASD status (Figures 1 and 2). For both bladder training (N=467 males, 143 females) and bowel training (N=464 males, 135 females), there is clear separation between survival curves for males and female strata and virtually no overlap in confidence bands ($p<0.001$), confirming a significant difference in sex-related training success across all ages, with females trained at much earlier ages (Figures 1a and 2a). Females were 3 times more likely than males (using the hazard ratio) to achieve bladder and bowel training at any given age. Females with FXS were close to achieving toileting milestones at the same general ages as would be expected for typically developing females.

For both bladder and bowel training, survival curves by combinations of sex and co-morbid diagnosis of ASD (males with and without ASD, females with and without ASD) showed significant differences between strata, either when ASD was diagnosed by DSM5 criteria applied by the clinician or by meeting both SRS and SCQ cut points optimized for FXS (both at $p<0.001$; data from latter definition not shown in charts). ASD diagnosis was a strong discriminator for the risk for achievement of toileting milestones using either method of diagnosis, which produced very similar survival curves. The largest gap was between females without ASD and males with ASD, with females with ASD and males without ASD having similar curves. As children approach 6 years of age, there is no overlap between the confidence bands, indicating a clinically important and statistically significant difference when ASD status is taken into consideration, particularly for males and for both bladder and bowel training. When analyzed separately, females with and without co-morbid ASD did not show significantly different rates of training; however rates of training were significantly different between groups of males without ASD and males with ASD (Figures 1b, 2b). In fact, only about 70% of males with FXS and comorbid ASD achieved the bladder and bowel training milestones by age 16.

DISCUSSION

This is the first study to examine the age spectrum of toilet training and factors associated with severe delay in TT in individuals with FXS. From the data presented it is clear that many individuals with FXS experience substantial delay in TT for both bladder and bowel.[4,5] Delays of this magnitude put a considerable burden on families raising a child with FXS, and can limit educational and vocational options for the individual. The expected relationship between sex and toilet training was supported by our findings of females being toilet trained earlier than males. This is a result of the milder phenotype in females, who tend to have higher cognitive functioning, better language skills and fewer severe behavior problems, due to compensatory effects of the normal (unaffected) X chromosome expressed in a percent of neurons. It is important to note that in the multivariate analysis, the effect of sex became non-significant when language level, level of ID, ASD status, and severe behavior were accounted for in the model, suggesting that the effect of sex is due to a less impaired phenotype among females, who are typically ‘protected’ by the presence of an intact X chromosome.

In bivariate analyses, severe delay in TT was associated with low or nonverbal language abilities, lower IQ, presence of ASD, and severe behavior in areas of both irritability and hyperactivity. The medical factors and medication use were significant in multiple logistic regression models, probably due to the strong effect of other, correlated covariates, although there were trends toward relationships with presence of seizures, use of anti-convulsants for seizures and use of alpha-agonists, mood stabilizers, and anti-psychotics. This seems less likely to be related to side effects of medication, but rather to the tendency of patients on these kinds of medication to have a more severe behavioral phenotype, and be more likely to have ASD.[32] When multiple regression models were used to sort out which factors were independent predictors of severe toileting delay, only lower language milestones, ASD co-morbid diagnosis, and irritable behavior were independent predictors of severe delay in toileting.

Indeed, multivariate analyses and the Cox proportional hazards models show that in males with FXS, language/communication milestones are the largest predictor of TT, with ASD diagnosis and irritable behavior (based on ABC^{FX} scores) also contributing. Other functional measures do not add to these factors. In females, who are much less likely to be diagnosed with ASD, higher language level is a strong predictor of TT, but higher cognitive level is also important for bladder training and absence of ASD for bowel training. Overall, this study provides the first evaluation of factors associated with TT in an IDD population, and the results identify language development as the single factor most strongly associated with achieving TT in such as population of FXS, confirm the critical nature of language and communication skills to TT and define the patient groups at highest risk of very delayed or even the failure to achieve TT. This group can thus be potentially targeted for tailored clinical interventions.

Survival curves are significantly different for females, males without ASD, and males with ASD. These curves are helpful for understanding expected timing of training given sex and ASD diagnosis. The multivariate analyses and survival curves are helpful also in designing strategies to improve TT and identifying groups in whom earlier more intensive intervention may be required to achieve TT. The analyses presented here for the FXS population can serve as a model for other IDD populations, for whom factors influencing TT are expected to be similar to FXS.

In these analyses the results based on clinician diagnosis of ASD was very similar to results based on combined SCQ and SRS-2 cut points optimized for FXS[30], suggesting that the new cut points are an important alternative in the absence of expert clinician diagnosis. Indeed when the original SRS-2 and SCQ cut points are used (data not shown), results are quite different from clinician diagnosis of ASD, as a very high percent of patients with FXS meet criteria for ASD according to these cut offs, which do not take into account the ID inherent in FXS. In clinical practice, the use of clinician diagnosis using DSM criteria for ASD is typical given the lack of feasibility of using the Autism Diagnostic Interview-Revised and/or the Autism Diagnostic Observation Schedule in a busy clinical setting. However, there may be some lack of sensitivity and specificity in diagnosis with this approach, and these patients could be referred for a proper gold standard assessment..

Limitations of this study are primarily centered on the fact that the data were collected via a parent report survey based on parental recollection at the time of the FORWARD assessment. There is therefore a potential for recall error, especially when there is a substantial latency between the age at which the individual is first evaluated and the age at which milestone achievement was reported to have occurred. Finally, inter-rater and inter-clinic reliability of ASD diagnosis has not been established in this study, so it is possible that there is diagnostic inconsistency in ASD diagnosis between and within clinics. However, to the extent that any of the above factors results in measurement error, the bias would be toward the null hypothesis, that is toward less difference between groups than actually exists. In other words, the differences between males and females, and the effects of language and ASD on TT could well be even greater than the significant effects we report. Additionally, we lacked a cohort with ASD but not FXS. Comparison of cohorts with FXS and no ASD and ASD without FXS would further clarify the role of ASD in toilet training delay.

The average age of the group (at the time the form was completed) that toilet trained by 10 was significantly greater than the group that did not toilet train by 10, for both bladder and bowel training. Although this could be related to recall inaccuracy, toileting tends to be a milestone that families remember well as they work so hard to achieve this goal. In a small study of parental recall at age 4–5 of developmental milestones in typically developing children, there was 100% agreement for bladder and bowel training (the best agreement among the milestones).[32] In another study of recall of milestone achievement at the child ages of 2, 3, 5, and 9 in an autism referral group, average ages of bladder training (bowel training was not asked) did not differ significantly (2 week average difference) across time points of recall.[33] In a study of accuracy of maternal reporting of milestones against the Bayley Scales of Infant Development at age 3, both bladder and bowel training were statistically significantly correlated.[34] In general, age at attendance may be due to issues of severity. Less severe patients are more likely to be living at home and easier to get to appointments, while more severe patients are less likely to be seen when older because they have been placed in a group home and thus less likely to come to FXS clinics. Severe behaviors that may be associated with toileting problems will also tend to make it difficult for families to get the affected older individuals in to FXS clinics.

The results presented here can be used to advance research on the effectiveness of targeted approaches to TT for those who present with a profile suggesting later onset of successful training. Given that ultimate successful TT has such broad impact on adaptive and community functioning in adult life, advancing this area of study is crucial. Additionally, it will be important for clinicians to develop and to work with families to design approaches specifically for individuals for whom traditional definitions of being toilet trained are unlikely. Several different approaches to TT have been researched within the IDD population including but not limited to; graduated guidance, reinforcement-based training, scheduled sittings, elimination schedules, punishment, hydration, manipulation of stimulus control and priming and video modeling.[11] The individual's developmental profile, however, was rarely used to inform the selection of the approach, which could serve to limit success. The authors propose that relative strengths and weaknesses of the individual should be taken into account when determining the approach utilized in order to increase the likelihood of success and to decrease the stress on both the individual as well as the family. Using individual strengths to address challenges and providing appropriate supports to accommodate relative weaknesses will result in better outcomes.

As an example, in the case of FXS, language is considered to be a central factor in TT. Priming using language heavy books or lengthy conversations should be contraindicated. Punishment procedures that involve language and/or extensive multistep processes of restitution, including cleaning up, putting the soiled clothes in the laundry, etc. may cause too much frustration and, without effective language skills, may result in a lack of associating the punishment to the toileting accident; this would, in turn, eliminate any positive effect of the punishment. Additionally, previous recommendations by the FXCRC and the literature recommend starting with bowel training rather than bladder training, however the data in this report are not consistent with bowel training occurring first.[29,30,35,36] Bladder training occurs before bowel training at least for some individuals with FXS, and based on the predictors identified in this paper, bladder training can be addressed first for children who seem predisposed to this. This suggests that the utilization of elimination schedules as a foundational component of any TT approach with individuals with FXS is essential. Elimination schedules identify the patterns of elimination which can be used to inform a scheduled sitting approach in which individuals are placed on a toilet for set amounts of time and rewarded when they void their bladder or bowels.[37] The schedule increases the likelihood of "catching" the child at the right time so that they void when placed on the toilet. Scheduled sitting could be particularly effective because language could be diminished or virtually eliminated with the implementation of a picture schedule, a visual mechanism for marking time, and simple sign language for communicating success and completion. Additionally, the use of video modeling or priming using picture books or social stories could be very effective. This strategy illustrates how the FXS profile can and should be used to inform training approach and how both holistic and behavioral methods that have proven to be effective within the IDD population can be utilized..

The mechanisms that result in delayed toilet training in FXS remain unclear but, in addition to the factors that have been identified in this paper, inherent symptoms associated with FXS including anxiety, low core muscle tone, and gravitational insecurity may make it difficult for these children to have a bowel movement on the toilet.[38] Thus, it is important to consider accommodations and modifications to the environment that take into consideration the known behavioral phenotype of individuals with FXS. Modifying the bathroom environment by providing the child a stool to rest their feet on and an insert for the toilet might make some feel more stable. Decreasing the sensory stimuli such as lotions, potpourri, and candles might also be effective for those with sensory processing issues. Technological aides for detecting beginning urination could also be considered. Additionally, RTT when applied too early may cause increased anxiety and should be monitored.

The Kaplan-Meier survival curves offer a simple graphic presentation to families that should be helpful in understanding the timing of delays in training that are typical for males with FXS, and milder delays for females with FXS. In addition to reducing parental frustration and creating realistic expectations, these findings should promote a thoughtful, informed, encouraging response from practitioners and encourage a more positive perception of the child regarding the toileting experience. Information in this report should be shared beyond the community of clinicians. Early intervention specialists and preschool teachers are often tasked with assisting in TT. Increasing knowledge of professionals about anticipated age ranges based on the survival curves in Figures 1 and 2 will be important for the quality of life for both the individual child as well as the family by setting appropriate expectations and by motivating the introduction of alternative TT practices. Based on the data in this report, it will take several extra years for many children with FXS to be successfully toilet trained[4,5], particularly males with poor language skills and autism. Focusing on the foundational skills for daily living related to TT such as teaching the child to remove clothes, to sit on the toilet for several minutes two to three times per day, and to learn to flush and wash hands might be an appropriate strategy for parents and teachers, rather than expecting successful TT during the preschool and early elementary school years. To aid families, clinicians, and related service providers, continued research should be conducted on effective approaches for those individuals with profiles that suggest significant delays in TT. TT continues to be such an issue for families and caregivers and if approaches can be targeted to the individual or the group of individuals with a specific diagnosis then perhaps the time to training can be diminished and the stress on all involved decreased. The data in this report serves as a seminal reference for assessing the effectiveness of new toileting interventions in future research.

ACKNOWLEDGEMENTS

This publication was supported by cooperative agreements #U01DD000231, #U19DD000753 and # U01DD001189, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services. The authors thank Walter Kaufmann MD for his parallel work on the method for adapting the cut points in the SRS and SCQ to improve the accuracy of these instruments for ASD diagnosis in FXS.

Sources of Support: Work on this publication was supported by cooperative agreements #U01DD000231, #U19DD000753 and # U01DD001189, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

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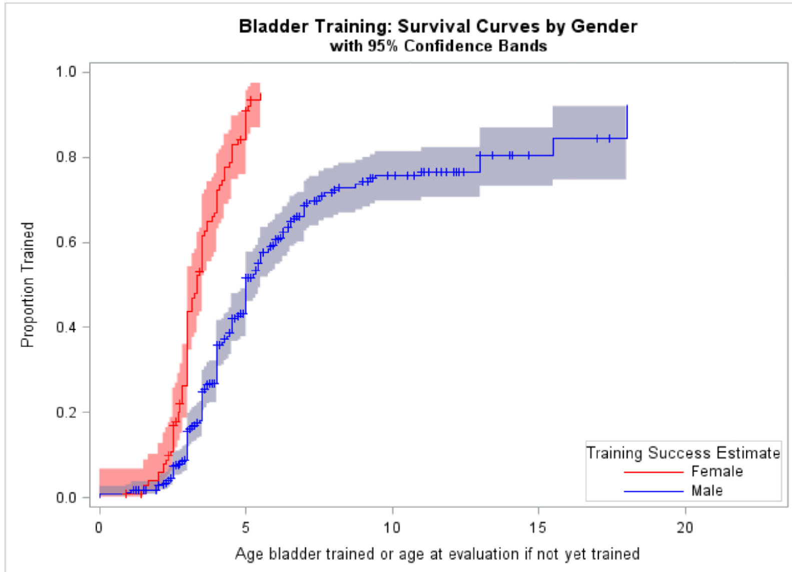
(a) by sex



(b) by sex and ASD status

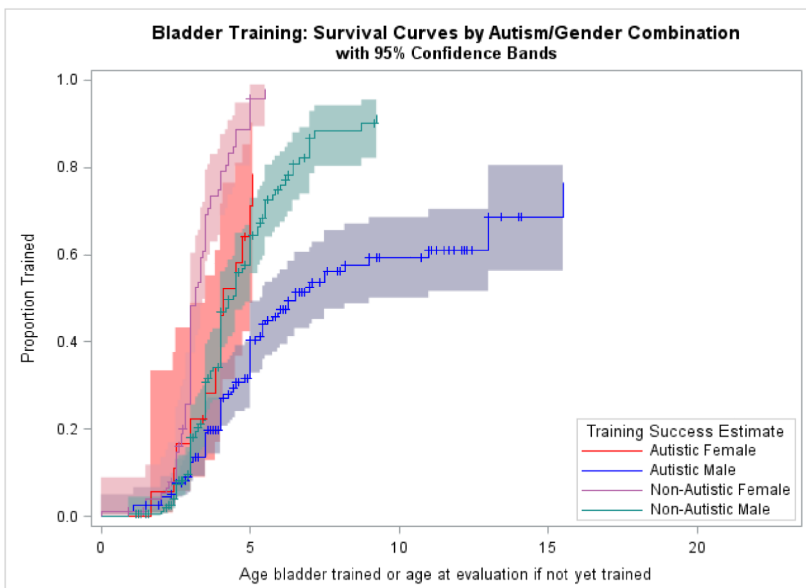
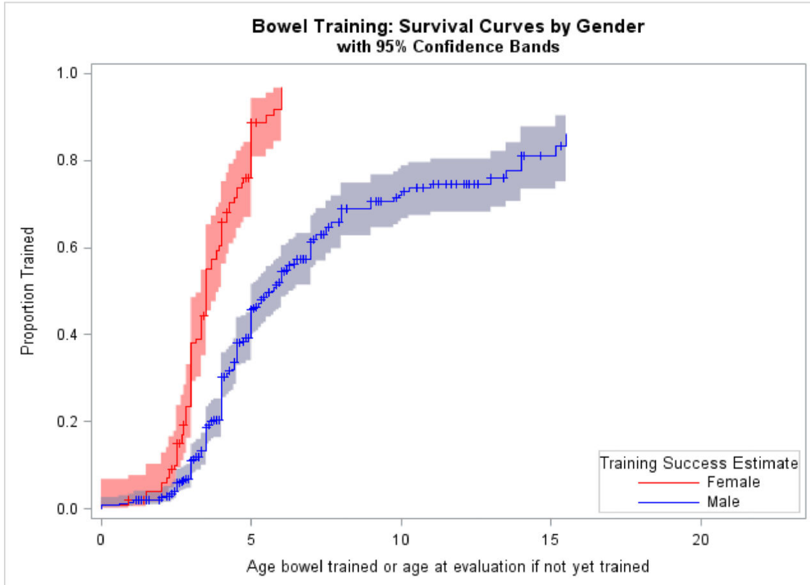


Figure 1.

Survival Curves of Time to Bladder Training (n=486)

a) by sex



b) by sex and ASD status

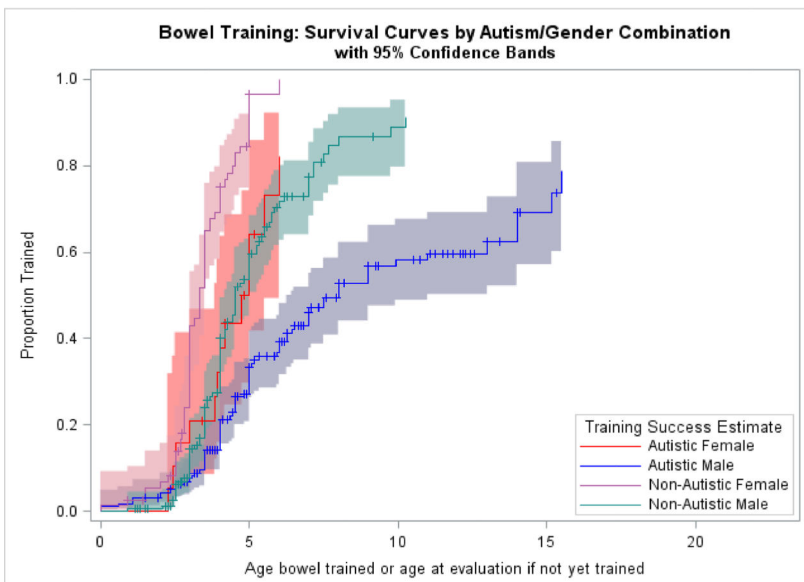


Figure 2.

Survival Curves of Time to Bowel Training (n=472)

Table 1.

Characteristics of Total Analyzed Sample (N=633)

	n (%)[*]
Sex (male)	485 (77%)
Race-ethnicity: Hispanic	74 (12%)
Non-Hispanic White	488 (77%)
Non-Hispanic Black/African American	40 (6%)
Asian	23 (4%)
Other	8 (1%)
Age at clinical evaluation (median [IQR])	10.42 [6.08–15.58]
Ever Seizures	75 (12%)
Any asthma	27 (4%)
Language Milestones	
Small number of words or less	119 (19%)
Series of single words or 2-word combinations used	71 (11%)
Phrases/sentences of 3 words or more	439 (70%)
Can the child write his/her first and last name from memory?	
No	86 (14%)
Typing	14 (2%)
By hand	196 (32%)
Both	317 (52%)
ASD diagnosis by Clinician	237 (42%)
ASD diagnosis by SRS/SCQ DFV criteria[1]	203 (41%)
Level of Intellectual Disability	
No ID/Borderline ID/Developmental Delay	162 (27%)
Mild ID	143 (24%)
Moderate	254 (43%)
Severe or profound	33 (6%)
Current symptom severity (only for subject on medication) (N=385)	
Normal to mild symptom/behavior	85 (22%)

	n (%)*
Moderate to severe symptom/behavior	300 (78%)
Subject on any alpha-agonists	101 (16%)
Subject on any anti-psychotics	117 (18%)
Shows signs of hyper arousal	556 (91%)
ABC Irritability Subscale (mean ± sd)	32.91 ±12.75
ABC Hyperactivity Subscale (mean ± sd)	20.93 ±7.86

[*] Percentages are calculated based on the number of total responses for each item in a category; category n may be slightly lower in some cases than n indicated in table header, due to missing data.

[1] ASD Diagnosis by SRS/SCQ DFV criteria (SCQ ≥ 8 and SRS ≥ 65 versus SCQ < 8 and SRS < 65)

Table 2.

Characteristics of Participants Toilet Trained and Not Trained by Age 10

	Bladder trained (N=313)			Bowel trained (N=300)		
	YES (n=274)	NO (n=39)	p	YES (n=249)	NO (n=51)	p
Demographic and other characteristics	n (%)*	n (%)*		n (%)*	n (%)*	
Sex (male)	204 (74.4)	38 (97.4)	<0.001	187 (75.1)	50 (98.0)	<0.001
Race/ethnicity (white)	223 (81.4)	33 (84.6)	0.24	202 (81.7)	43 (84.3)	0.24
Age at clinical evaluation(mean ± std)	15.88 [12.83–20.75]	12.25 [11.25–15.50]	<0.001	15.92 [13.00–21.00]	12.50 [11.58–15.83]	<0.001
Ever seizures	43 (15.7)	10 (25.6)	0.12	38 (15.3)	14 (27.4)	0.04
Any asthma	8 (2.9)	4 (10.3)	0.03	6 (2.4)	6 (11.8)	0.002
Language Milestones			<0.001			<0.001
Small number of words or less	8 (2.9)	17 (43.6)		7 (2.8)	17 (33.3)	
Series of single words or 2-word combinations used	15 (5.5)	9 (23.1)		15 (6.0)	9 (17.6)	
Phrases/sentences of 3 words or more	249 (90.9)	13 (33.3)		225 (90.4)	25 (49.0)	
Can the child write his/her first and last name from memory?			<0.001			<0.001
No	56 (20.4)	29 (74.4)		49 (19.7)	33 (64.7)	
Typing	11 (4.0)	1 (2.6)		8 (3.2)	4 (7.8)	
By hand	55 (20.1)	3 (7.7)		54 (21.7)	4 (7.8)	
Both	144 (52.6)	5 (12.8)		132 (53.0)	7 (13.7)	
ASD diagnosis by clinician	94 (34.3)	29 (74.4)	<0.001	82 (32.9)	39 (76.5)	<0.001
ASD diagnosis by SRS/SCQ DFV criteria[1]	87 (31.8)	25 (64.1)	<0.001	77 (30.9)	33 (64.7)	<0.001
Level of Intellectual Disability			<0.001			<0.001
No ID/Borderline ID/ Developmental Delay	44 (16.1)	0 (0.0)		39 (15.7)	0 (0.0)	
Mild ID	70 (25.5)	3 (7.7)		63 (25.3)	5 (9.8)	
Moderate	128 (46.7)	23 (59.0)		118 (47.4)	29 (56.9)	
Severe or profound	9 (3.3)	11 (28.2)		7 (2.8)	12 (23.5)	
Current symptom severity (only for subject on medication) (N=385)			<0.001			<0.001
Normal to mild symptom/ behavior	57 (27.8)	2 (5.5)		51 (27.1)	2 (4.4)	
Moderate to severe symptom/ behavior	148 (72.2)	34 (94.4)		137 (72.9)	43 (84.3)	
Subject on any alpha-agonists	46 (16.8)	14 (35.9)	0.005	40 (16.1)	17 (33.3)	0.004
Subject on any anti-psychotics	65 (23.7)	17 (43.6)	0.008	58 (23.3)	22 (43.1)	0.003
Shows signs of hyper arousal	241 (88.0)	38 (97.4)	0.04	220 (88.3)	49 (96.1)	<0.001
ABC^{FX} Irritability Score (mean ± sd)	29.3 ± 11.4	39.5 ± 13.3	<0.001	29.0 ± 11.1	39.0 ± 14.1	<0.001

	Bladder trained (N=313)			Bowel trained (N=300)		
	YES (n=274)	**NO (n=39)**	**p**	**YES (n=249)**	**NO (n=51)**	**p**
Demographic and other characteristics	**n (%)***	**n (%)***		**n (%)***	**n (%)***	
ABC^{FX} Hyperactivity Score (mean ± sd)	17.6 ± 6.6	24.5 ± 7.2	<0.001	17.6 ± 6.6	23.6 ± 7.2	<0.001

*Percentage interpretation (example): 74.4% of those who were bladder trained by age 10 were male; among those not bladder trained by age 10, 97.4% were male. Percentages are calculated based on the number of total responses for each item in a category; category n may be slightly lower in some cases than n indicated in column header, due to missing data.

[1]ASD Diagnosis by SRS/SCQ DFV criteria (SCQ ≥ 8 and SRS ≥ 65 versus SCQ < 8 and SRS < 65)

Table 3.

Logistic Regression Models: Predictors of Toilet Training by Age 10

Odds of bladder training by age 10 (n=313)	**Adjusted logistic regression model**	
	Odds Ratio (95% CI)	**p**
Female vs Male	1.97 (0.21, 18.43)	.55
Ever had seizures (Yes vs No)	1.07 (0.31, 3.65)	.91
For each reduction in level of intellectual disability	1.58 (0.69, 3.78)	.28
For each additional language milestone achieved	4.88 (2.63, 9.08)	<0.001
Autism by clinician diagnosis(No vs Yes)	2.17 (0.66, 7.14)	.20
For each unit decrease in ABC^{FX} Irritability Score	1.05 (1.01, 1.10)	.01
Odds of bowel training by age 10 (n=300)	**Adjusted logistic regression model**	
	Odds Ratio (95% CI)	**p**
Female vs Male	2.94 (0.33, 25.96)	.33
Ever had seizures (Yes vs No)	1.02 (0.34, 3.03)	.98
For each reduction in level of intellectual disability	2.17 (0.95, 5.00)	0.07
For each additional language milestone achieved	3.40 (1.88, 6.14)	<0.001
Autism by clinician diagnosis(No vs Yes)	2.78 (0.99, 7.69)	.05
For each unit decrease in ABC^{FX} Irritability Score	1.04 (1.00, 1.07)	.04

Table 4.

Cox Proportional Hazard Models: Predictors of Toilet Training (Age at Evaluation >1)

Bladder Training	**Males (N=366)**		**Females (N=120)**	
	Hazard Ratio (95% CI)	**p**	**Hazard Ratio (95% CI)**	**p**
For each reduction in level of intellectual disability	1.12 (0.93, 1.33)	0.23	1.54 (1.16, 2.04)	0.003
For each additional language milestone achieved	2.12 (1.66, 2.71)	<0.001	1.92 (1.06, 3.47)	0.03
Autism by clinician diagnosis (No vs Yes)	1.56 (1.16, 2.08)	0.003	1.39 (0.89, 2.38)	0.23
For each unit decrease in the ABC^{FX} Irritability Score	1.01 (1.00, 1.02)	.04	1.02 (1.00, 1.04)	0.05
Bowel Training	**Males (N=361)**		**Females (N=111)**	
	Hazard Ratio (95% CI)	**p**	**Hazard Ratio (95% CI)**	**p**
For each reduction in level of intellectual disability	1.22 (0.78, 1.91)	0.23	1.30 (0.99, 1.69)	0.06
For each additional language milestone achieved	2.03 (1.56, 2.64)	p<0.001	2.10 (1.11, 3.97)	0.02
Autism by clinician diagnosis (No vs Yes)	1.75 (1.30, 2.38)	0.003	1.92 (1.05, 3.57)	0.03
For each unit decrease in the ABC^{FX} Irritability Score	1.01 (1.00, 1.02)	0.04	1.01 (0.99, 1.03)	0.27