Supplementary methods

Search strategy

A focused literature review (FLR) was performed to retrieve publications that would allow the creation of a model to explore the effect of abobotulinumtoxinA (aboBoNT-A) injections on long-term outcomes in post-stroke patients with spasticity.

The objectives of the FLR were as follows.

- To quantify the effect of botulinumtoxinA (BoNT-A) on measures of disability for patients with post-stroke spasticity (PSS).
- To quantify the association between measures of disability and long-term outcomes, such as death and secondary cardiovascular events, in stroke survivors.

Searches for publications reporting the effect of BoNT-A injections on disability and functional outcomes were set up to retrieve:

- systematic literature reviews
- randomized clinical trial (RCT) publications
- prospective and retrospective studies

Searches were performed to retrieve studies investigating any type of disability or functional outcomes used to measure the efficacy of BoNT-A injections in PSS. Searches were not restricted to the most common outcomes (Table SI).

For studies on long-term outcomes, searches were performed using disability and functional outcomes identified during the first step of the FLR. In addition, owing to scarcity of data specific to post-stroke patients with spasticity, searches for long-term outcome studies were broadened to studies in both post-stroke and non-stroke patients.

Searches were performed in PubMed, Cochrane Library and Google search engine (1–3).

Effect of BoNT-A injections on disability and functional outcomes

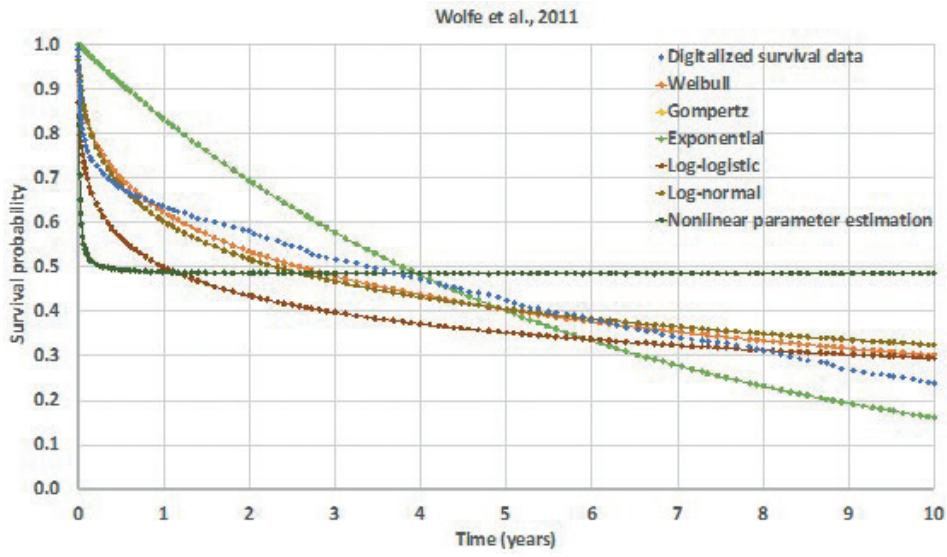
In total, 43 publications reporting the effect of BoNT-A injections on functional outcomes were retrieved with the FLR and by additional post hoc manual search. Most of the publications were RCTs (n = 35) and only 8 publications were not RCTs. All studies were conducted in adults with PSS, or in a mixed population of patients with PSS and/or traumatic brain injury (n = 6 publications). The majority of studies investigated the effect of BoNT-A injections in upper-limb spasticity (n = 28). The remaining studies assessed the effect of BoNT-A injections in patients with lower-limb spasticity (n = 13) or both upper- and lower-limb spasticity (n = 2).

Variable doses (50–1,500 U) and types of BoNT-A (aboBoNT-A, incobotulinumtoxinA and onabobotulinumtoxinA) were administered to patients included in the reported studies. Twelve publications assessed the use of BoNT-A injections as the only intervention and 34 publications reported the effect of BoNT-A injections when added to the standard rehabilitation therapy (RT). The maximum number of injections used in the reported studies varied from 1 to 5, with only 1 study not specifying the number of injections received by patients (4). Evidence for 11 functional outcomes was found in the available literature: 2- or 6-minute walking test (2/6MWT; n = 6 publications), Berg Balance Scale (BBS; n=3 publications), Barthel Index or Modified Barthel Index (BI/mBI; n = 10 publications), Custom Disability Scale (n = 2 publications), Disability Assessment Scale (DAS; n = 10 publications), Functional Independence Measure (FIM; n = 6 publications), gait speed (n = 10 publications), Goal Attainment Scale (GAS; n = 5 publications), stepping rate (n = 1 publication), Timed-up and Go test (TUG; n = 4 publications), and the visual analogue scale (VAS; n = 1 publication).

From the 43 publications reporting the effect of BoNT-A injections on disability or functional outcomes, only 21 publications reported complete data to summarize the effect of BoNT-A. De novo meta-analyses were performed using the random effect model (to account for the heterogeneity of the evidence) to compute the summary effect of BoNT-A injections on the 6MWT, BBS, BI, DAS, FIM, gait speed and TUG outcomes. Summary effects for the control intervention were computed for the BI, FIM, BBS, DAS and gait speed outcomes as properly controlled studies were available (Table SII). As the objective of the model is to compare RT and aboBoNT-A injections with RT alone, the measurement (also known as effect size) selected for the meta-analysis was the mean difference (MD) between last follow-up (up to 8 weeks) and baseline measurements.

Overview of the long-term outcome studies identified in the FLR

The FLR identified 15 distinct studies that assessed the relationship between disability or functional outcomes, and long-term outcomes (5–19). Although none of the 15 studies mentioned the inclusion of patients



with PSS, 5 studies comprised exclusively post-stroke patients (9–11, 14–16).

Studies of post-stroke patients assessed the relationship between functional outcomes and all-cause mortality, incidence of cardiovascular events, stroke recurrence or the risk of falls (Table SIII).

In prospective and retrospective studies that were not restricted to stroke patients, the main functional outcomes associated with long-term outcomes were gait speed, the corridor walk test, the BI (at hospital admission) and the TUG. It is worth mentioning that the study that assessed the relationship between gait speed and all-cause mortality, explicitly excluded patients with known decreased ability to walk, such as patients with disabling stroke (5) (Table SIV).

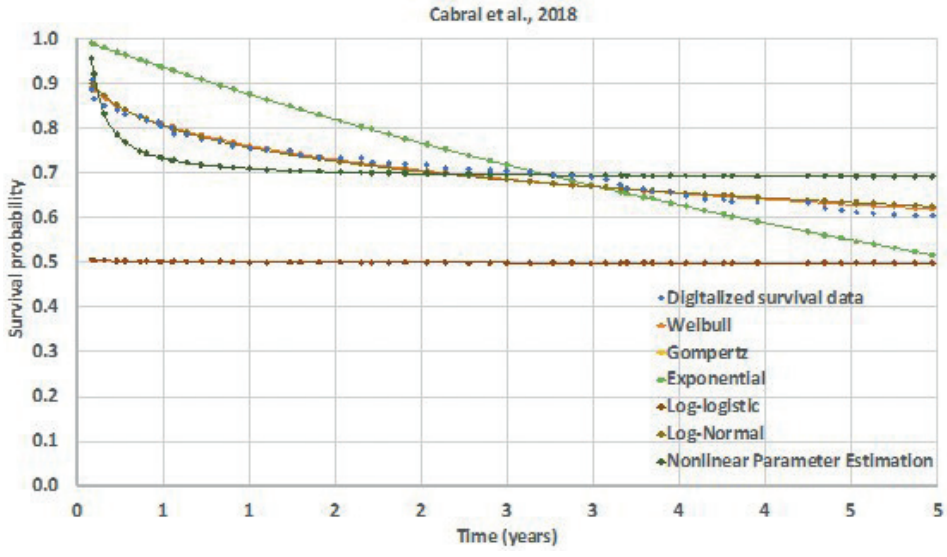
Calculation of the effect of an intervention on all-cause mortality

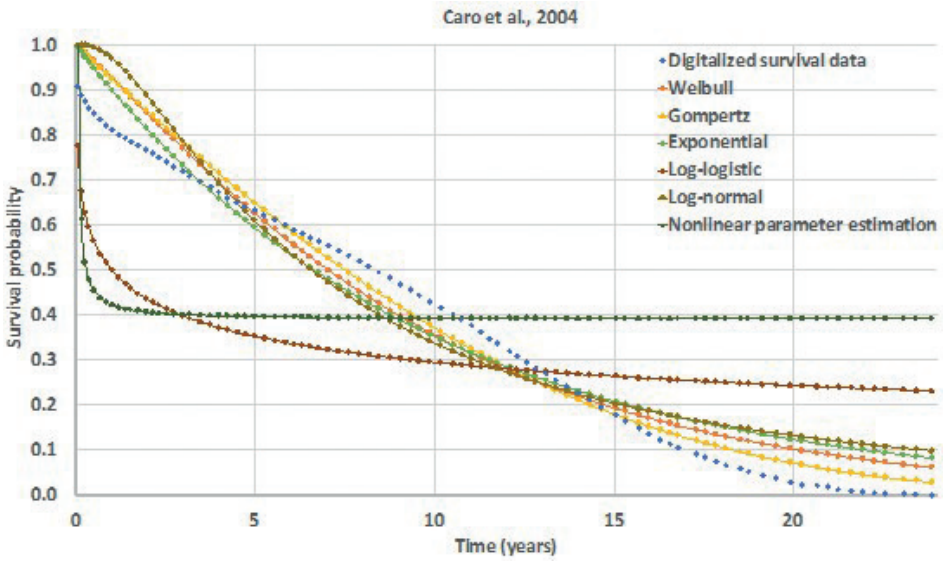
The effect of interventions, aboBoNT-A injections and RT, and RT alone on long-term outcomes were modelled using the hazard ratios (HR) associated with long-term outcomes retrieved from the FLR.

Briefly, the HRs for each intervention were calculated using this formula:

$$HR_{intervention} = HR^{Summary\ effect\ of\ the\ intervention} \quad (1)$$

As in the Cox regression model, the HR is calculated as the exponential of the product between the β coefficient and the continuous variable, and the exponential





of a product is equal to the exponential of the first value (β) powered to the second value (value of the continuous variable).

Modelling of survival data for each intervention

For each intervention, the model computes a new scale parameter (for Weibull and Gompertz survival functions) with the new HR calculated in equation 1.

For the Weibull distribution, the survival distribution S(t) (with scale parameter b and shape parameter a) is given by:

$$S(t) = e^{-(b*t)^a} \quad (2)$$

And the hazard function h(t) is:

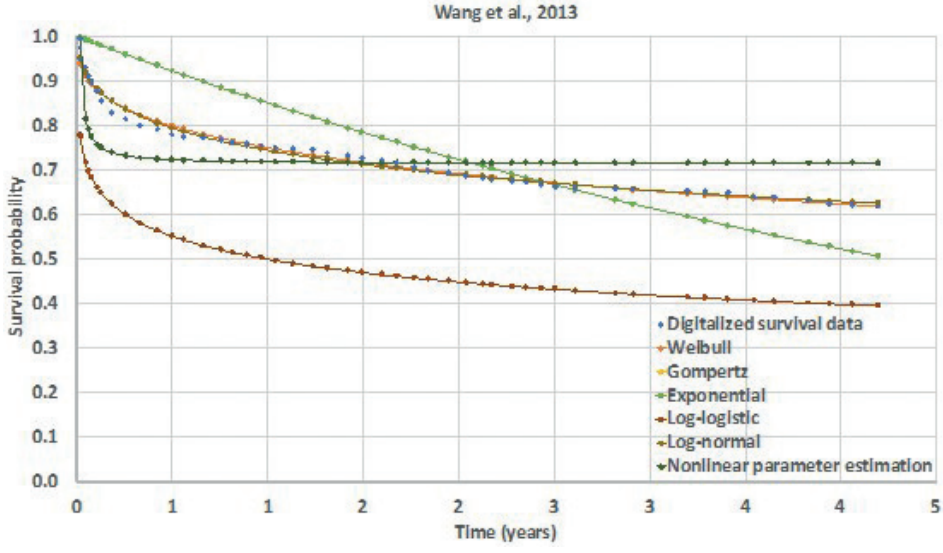
$$h(t) = b*a*\left(b*t\right)^{a-1} \quad (3)$$

The HR is equal to (assuming the same shape of Weibull distributions in intervention and base hazard function):

$$HR = \frac{h_1(t)}{h_0(t)} = \frac{b_1*a*\left(b_1*t\right)^{a-1}}{b_0*a*\left(b_0*t\right)^{a-1}} \quad (4)$$

$$= (\frac{b_1}{b_0})^a \quad (5)$$

Thus, the new scale parameter for the Weibull survival function is given by:



$$b_1 = b_0 \sqrt[a]{HR} \quad (6)$$

For the Gompertz distribution, the survival distribution S(t) (with scale parameter b and shape parameter a) is given by:

$$S(t) = \exp(\frac{b}{a}(1 - e^{at})) \quad (7)$$

And the hazard function h(t) is:

$$h(t) = be^{at} \quad (8)$$

The HR is equal to (assuming the same shape of Gompertz distributions in and base hazard function):

$$HR = \frac{h_1(t)}{h_0(t)} = \frac{b_1 * e^{at}}{b_0 * e^{at}} \quad (9)$$

$$= \frac{b_1}{b_0} \quad (10)$$

Thus, the new scale parameter for the Gompertz survival function is given by:

$$b_1 = b_0 * HR \quad (11)$$

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